The Chemistry of Azetidin-3-ones, Oxetan-3-ones, and Thietan-3-ones

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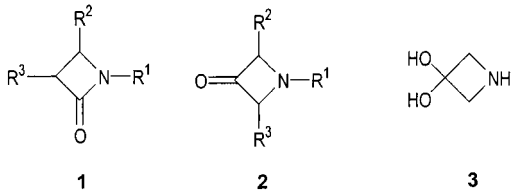
I. Introduction

The aim of this review is to cover the literature of 3-azetidinones, 3-oxetanones, and 3-thietanones, including partially 3-thietanone-1-oxides and 3-thietanone-1,1-dioxides. Each of these small heterocyclic ring systems will be treated in detail in separate chapters, the main lines being at first a short statement about structural information of the heterocyclic system concerned, second, an overview of the methods available for the synthesis of the particular heterocycle, and finally, a discussion on the reactivity of the ring system.

II. The Chemistry of Azetidin-3-ones

Among azetidine derivatives, compounds carrying a carbonyl group at either position 2 or position 3 occupy a special place (Figure 1). The former are



1 2 3

Figure 1.

represented as β-lactams **1** (azetidin-2-ones), monobactam antibiotics, and natural bicyclic azetidin-2-one derivatives, e.g., penicillins, cefalosporins, thienamycins, etc.[1−17]

Much less widespread are azetidin-3-ones **2**, which are not yet found in nature. However, azetidin-3-ones have been proposed for use in the synthesis of other natural compounds of the azetidine series, in particular, 3-ethylideneazetidin-2-carboxylic acid (polyoximic acid), which is a part of the structure of the nucleoside tripeptide antibiotic polyoxines.[18−22] Very recently, 3,3-dihydroxyazetidine **3**, the hydrate of azetidin-3-one, was isolated from the supernatant of a culture of *Bacillus mesentericus*.[23] This azetidine **3** is a new growth-promoting factor, stimulating the growth of several strains of *Bifidobacterium*.[23]

The rare synthetic representatives of azetidin-3-ones can be mainly obtained by oxidation of azetidin-3-ols, ring contraction of pyrrolidin-3,4-diones, or aziridine ring expansion and intramolecular heterocyclization reactions (vide infra).

A. Structural Data

The four-membered azetidin-3-one ring has a nonplanar structure. The first X-ray investigation was carried out on 1-*p*-toluenesulfonyl-2-ethylazetidin-3-one **4** (Figure 2).[25] It was shown that the deviation of the nitrogen atom from the plane of the three-ring

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Nina Kuz'menok was born in 1953 in Belarus. She graduated with honors from the Belarus State University in Minsk in 1975 and worked as research associate with Prof. A. M. Zvonok at the Scientific Research Institute of Physical Chemical Problems of the Belarus State University. She obtained her Ph.D. degree in 1983. Since 1990, she has been an Assistant Professor at the Department of Organic Chemistry at the Belarus State University of Technology where she is presently working on organic synthesis of heterocyclic compounds.

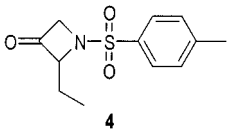
carbon atoms is 0.35 Å, and the inflection of the ring along the C−C line is 15°. Substituents at nitrogen and carbon C2 occupy the most favorable pseudo-equatorial positions.

It is important to notice that the lengths of the C−C bonds in the heterocyclic ring are not identical. In particular, the C3−C4 bond length is 1.505 Å, which corresponds to a Csp^3-Csp^2 bond, and the C2−C3 bond has a length of 1.554 Å. The bond angles C2−C3−O and C4−C3−O are equal, as well as the bond lengths N−C2 and N−C4. Apparently, the lengthening of the C−C bond in compound **4** does not result from a steric interaction between the ethyl substituent and the carbonyl group but reflects an electronic structure of the nonsymmetrically substituted azetidin-3-one.[25]

Quantum mechanical calculations of the azetidin-3-one structure, executed in the minimum basis OST-3GF, concerned mainly the elucidation of orbital interactions in small rings (data also included the

Alexander M. Zvonok was born in 1950 in Kletsk, Belarus. He finished his chemistry studies at the Belarus State University in 1972. In 1975, he received the doctoral degree (Ph.D.) in organic chemistry. From 1972 to 1991, he performed research as senior scientific researcher at the Belarus State University. He received his Doctor of Science (Dr.Sc.) degree in 1990 for his research on intramolecular cyclization of functional substituted epoxyketones. In 1992, he obtained the status of professor. Since 1991, he is the Head of the Department of Organic Chemistry at the Belarus State University of Technology. His current research interest concerns the development of new synthetic methodology of heterocyclic compounds. He has published about 200 scientific articles and owns 45 patents.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University. He performed postdoctoral research work at the University of Massachusetts, Harbor Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences at the University of Ghent, where he took up teaching positions since 1987. He is now Professor in organic chemistry at the latter institution. He was a guest-professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina), and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998. He is the author of 300 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals, and natural products, (2) flavor chemistry, and (3) the bioassay-guided isolation of physiologically active natural products from medicinal plants.

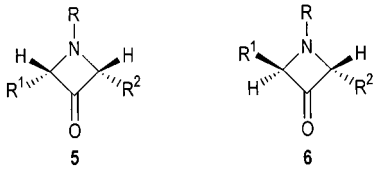


4

Figure 2.

oxetan-3-one and thietan-3-one structure).[26] The results obtained were in good agreement with photoelectronic and infrared spectroscopy data. IR absorption bands of the carbonyl group of azetidin-3-ones appear in most cases in the region of 1800−1835 cm^{-1}. The high frequencies of the C═O bond absorption underline the significant strain in the four-membered ring.[29,78] In addition, the stretching frequency does not change appreciably from that observed for cyclobutanone, underlining the fact that trans-annular participation (conjugation) is not that important. It is noted that p-orbital interactions through bonds in azetidin-3-ones play a not less essential role than trans-annular interactions through space.[26]

The absolute values of distant coupling constants (^4J) in ^{1}H NMR spectra, which are rather large, provide the evidence of this fact. Thus, in 2-methyl-, 2-ethyl-, and 2-benzyl-1-tosylazetidin-3-ones **6**, $^4J_{trans}$ values were of 2.70, 3.63, and 4.05 Hz, respectively.[25] Coupling constant values of $^4J_{cis}$ (see structure **5**) were smaller, i.e., ∼2.0 Hz (Figure 3).



5 **6**

Figure 3.

Contrary to planar three-membered heterocycles such as oxiranes and aziridines, where $^3J_{trans}$ is smaller than $^3J_{cis}$, in azetidines and azetidin-3-ones $^4J_{trans}$ is larger than $^4J_{cis}$. A distant coupling constant ^4J of the pseudoaxial proton 4a′ of the azetidine ring with the axial proton at position 1 of the *N*-cyclohexyl substituent appeared in 2-hydroxymethyl-2-methyl-4-(α-methoxybenzyl)-1-cyclohexylazetidin-3-one.[27] In the case of *N*-protected (Boc or *Z*)-2-alkyl- or 2-(arylmethyl)azetidin-3-ones, also a W-coupling in the order of 4.2−4.4 Hz has been observed between H−C2 and H−C4 on the same side of the ring.[28]

The mass spectra of azetidin-3-ones have been investigated in detail.[30] It has been noted that the fragmentation of azetidin-3-ones is accompanied by an extrusion of carbon monoxide.[31] However, *N*-unsubstituted azetidin-3-ones may undergo the mass spectral fragmentation with the extrusion of a ketene unit.[30] The character of the mass spectra of azetidin-3-ones is determined by the ionization conditions. In most cases, under the conditions of electron impact, it is possible to detect the molecular ion peak. However, for *N*-(arenesulfonyl)azetidin-3-ones, the molecular ion peak appears for compounds carrying an electron-donating substituent in the benzene ring. Initially, under electron impact conditions, azetidin-3-ones eliminate carbon monoxide, together with a four-membered ring cleavage and subsequent aziridinium ion-radical formation, which further decomposes by various paths, first of all with ring cleavage, and then with nitrogen substituent extrusion and elimination of other substituents, present in the molecule.[30] In mass spectra of azetidin-3-ones, recorded under chemical ionization conditions (2-methylpropene as reactant gas), the intensive signal of the protonated molecular ion is present. In contrast to mass spectra recorded under the conditions of electron impact, an ion-radical of *N*-unsubstituted azetidin-3-one or its structural isomer, i.e., aminomethyloxirene, is present.[30]

B. Synthetic Methods for Azetidin-3-ones

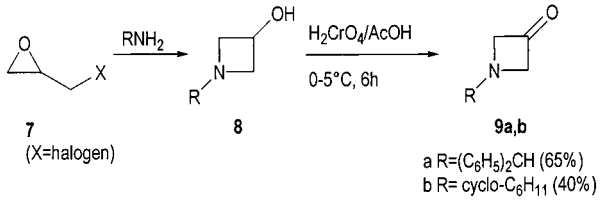
The synthetic methods for azetidin-3-ones can be grouped as follows:

1. Reactions based on carbonyl group generation in the azetidine ring
2. Reactions of intramolecular cyclization of acyclic carbonyl-containing substrates
3. 1,3-Dipolar cycloaddition of azomethin ylides or their synthetic equivalents to isonitriles

B.1. Carbonyl Group Generation in the Azetidine Ring

B.1a. Oxidation of Azetidin-3-ols. The most obvious way of carbonyl group introduction into an azetidine ring consists of the oxidation of the corresponding azetidin-3-ols **8**, of which the convenient synthesis is based on the reaction of primary amines with epihalohydrines **7**.[32−37] Although azetidin-3-ols **8** became available due to Gaertner's research,[32] the oxidation of these compounds was developed much later[31,38] since not all oxidizing agents seemed to be effective to perform this transformation. As a rule, the use of very reactive oxidizing agents resulted in cleavage and fragmentation of the azetidine ring, while in the case of mild reagents, oxidation did not proceed at all, and the starting alcohol was recovered. The Jones reagent was used successfully as an oxidant under carefully controlled conditions (Scheme 1).[31,38]

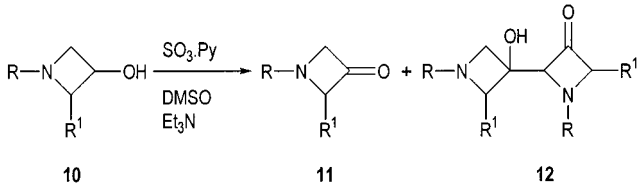
Scheme 1



The resulting 1-substituted azetidin-3-ones **9** are unstable at room temperature. However, compound **9a** can be kept at 0−5 °C during several weeks without noticeable decomposition, while compound **9b** under these conditions decomposed for more than 60% over a period of 12 h.

Azetidin-3-ones **11** were also obtained from the corresponding 3-azetidinols by oxidation with a complex of sulfur trioxide and pyridine in dimethyl sulfoxide in the presence of triethylamine (Scheme 2).[39,40] The reaction proceeded with good yield only in the case of 1-benzhydryl-3-azetidinone **11a** and

Scheme 2



1-cyclohexyl-2-phenyl-3-azetidinone **11b**. In all other cases, dimeric products **12** were formed, apparently in relation to the high reactivity of the intermediate azetidin-3-ones.[40] The dimeric compounds **12a**,**c**−**e** originated from an aldol-type condensation of the resulting products (Table 1). Steric hindrance, imposed by the substituents on nitrogen and C2 of the ring system, might play a role in these results.

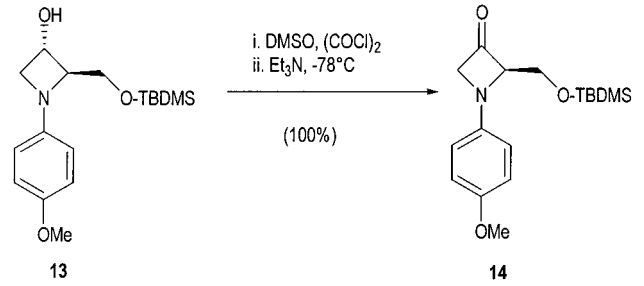
Table 1. Yields of Normal Oxidation Products 11 and Condensation Products 12

R	R^1	azetidin-3-one **11**	yield, %	aldol product **12**	yield, %
$(C_6H_5)_2CH$	H	a	80	a	16
cyclo-C_6H_{11}	C_6H_5	b	67	b	
t-C_4H_9	H	c		c	1.5
cyclo-C_6H_{11}	H	d		d	33
$C_6H_5(CH_3)CH$	H	e		e	30

The same reagent was used for the oxidation of *N*-benzoylazetidin-3-ol to the corresponding ketone, which was further transformed in 1-substituted-3-phenylazetidin-3-ols and their propionates, showing analgesic activity in warm-blooded animals.[41,42]

Other reagents that have been used for the transformation of azetidin-3-ols into azetidin-3-ones include trifluoroacetic anhydride, oxalyl chloride (Scheme 3), and phosphoric acid/dicyclohexyl-carbodiimide in dimethyl sulfoxide (Swern-type oxidations).[43−46]

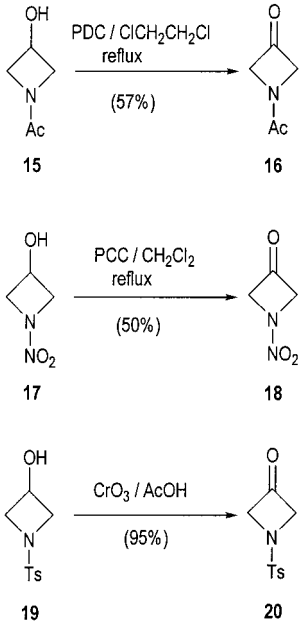
Scheme 3



Although it has been reported that several Cr(VI)-based oxidative methods fail for this type of conversion,[24] more recently, the oxidation of *N*-acetyl-3-hydroxyazetidine **15** and *N*-nitro-3-azetidinol **17** has been carried out using pyridinium dichromate and pyridinium chlorochromate, respectively.[47] Also chromium trioxide in acetic acid has been used with great success in the conversion of 1-tosylazetidin-3-ol **19** into 1-tosylazetidin-3-one **20** (Scheme 4).[48]

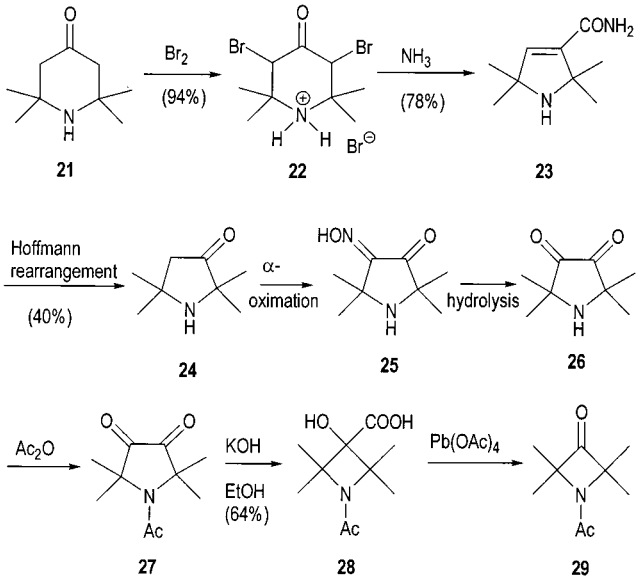
Apparently, the protection of the nitrogen atom of the azetidin-3-one ring with electron-withdrawing substituents, allowed the use of more general oxidative reagents for the conversion of the azetidin-3-ols to the corresponding ketones.

Scheme 4



B.1b. Oxidative Ring Contraction. The first representative of the azetidin-3-ones series, i.e., 1-acetyl-2,2,4,4-tetramethylazetidin-3-one **29**, was obtained by sequential ring contraction reactions of 2,2,6,6-tetramethylpiperidin-4-one **21** into 2,2,5,5-tetramethylpyrrolidin-3,4-dione **26**, which was transformed into 2,2,4,4-tetramethyl-3-hydroxyazetidin-3-carboxylic acid **28** by rearrangement, and the oxidation of the latter by lead(IV) acetate (Scheme 5).[29]

Scheme 5



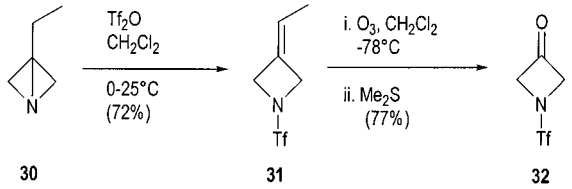
This described methodology for the synthesis of azetidin-3-ones was used many times by other authors.[49,50] The distinctions consist only in starting materials, where *N*-benzoyl derivatives instead of *N*-acetyl derivatives were applied, and in ways of obtaining the starting pyrrolidin-3,4-dione **26**. So the latter might be prepared by oxidation of the corresponding pyrrolidin-3-one **24** by selenium dioxide.[49]

An analogous oxidation reaction, using lead(IV) acetate, has been described.[51] 1-Benzoyl-3-hydroxy-2,2,4,4-tetramethylazetidin-3-carboxylic acid (the *N*-benzoyl analogue of compound **28**) was esterified using diazomethane and subsequently reduced under the action of lithium aluminum hydride. The resulting *N*-benzylazetidinediol was oxidized by lead(IV) acetate, resulting in 1-benzyl-2,2,4,4-tetramethylazetidin-3-one.[51] Drawbacks of this method are the rather long reaction pathway and the ability to synthesize only tetrasubstituted azetidin-3-one derivatives.

Azetidin-3-one **29** was also obtained as a side-product during the preparation of 1-acetyl-2,2,4,4-tetramethylazetidin-3-carboxylic acid via photolysis of 1-acetyl-4-diazo-2,2,5,5-tetramethylpyrrolidin-3-one.[50]

B.1c. Miscellaneous Reactions of Generation of the Carbonyl Group in the Azetidine Ring. Several reports appeared on the synthesis of azetidin-3-ones by ozonolysis of alkylidene azetidines **31** (Scheme 6).[52−56] The latter compounds can be ob-

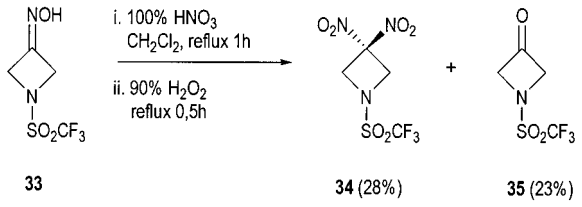
Scheme 6



tained by reaction of 1-aza-3-ethylbicyclo[1.1.0]-butane **30** with triflic anhydride[52,53] or benzoyltrifluoromethanesulfonate,[54] by reaction of *N*-nitro-3-ethylazetidin-3-ol with triflic anhydride in the presence of DMAP[53] or by reaction of *N*-(ethoxycarbonyl)-3-(bromomethyl)-3-chloroazetidine with potassium *tert*-butoxide[55] or by zinc promoted eliminative dehalogenation of *N*-acyl-3-(bromomethyl)-3-chloroazetidines.[56]

Subsequent ozonolysis of 3-alkylideneazetidines **31** yielded the corresponding azetidin-3-ones **32**. The same authors described the formation of azetidin-3-ones, e.g., **35**, by oxidative cleavage of the corresponding oxime **33** by sequential reaction with 100% nitric acid and 90% hydrogen peroxide (Scheme 7),

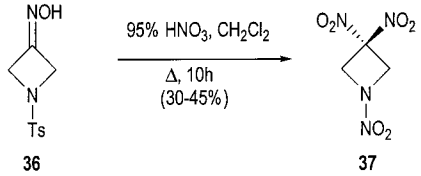
Scheme 7



the major reaction product being the 3,3-dinitroazetidine **34**.[53] Probably, under the applied conditions, the starting oxime **33** hydrolyzed again to the azetidin-3-one **35**.

This research has been done toward the synthesis of 1,3,3-trinitroazetidine **37** (TNAZ), a new energetic material with favorable detonation performance and other favorable properties, including low melting

Scheme 8



point, good thermal stability, low density, and low sensitivity (Scheme 8).[48,57,58] Approaches for the synthesis of TNAZ often start from the suitable azetidin-3-ones that are subsequently converted in the oximes and then treated with nitric acid. More recently, other methods and processes for preparing TNAZ and its intermediates, i.e., *N*-acetyl-3,3-dinitroazetidine (ADNAZ) and *N*-nitroazetidine were disclosed.[59,60] However, they do not concern the subject of this review.

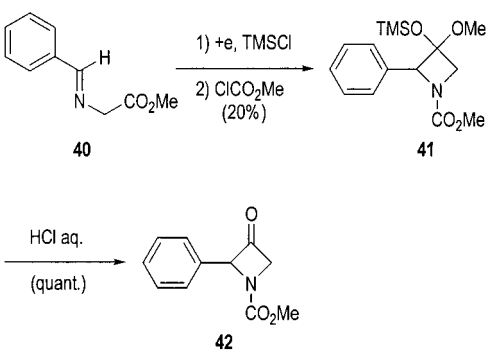
Another reaction pathway that involved azetidin-3-ones was obtained by flash vacuum thermolysis of 3-azido-2,2-dimethyl-3-phenylazetidine.[61] Thermolysis in the gas phase at 350 °C under a pressure of 1.5×10^{-3} Torr generated an intermediate nitrene that rearranged in two isomeric dihydroimidazoles and also yielded the *N*-phenylimine of 1-methoxycarbonyl-2,2-dimethylazetidin-3-one. The latter compound hydrolyzed to the azetidin-3-one upon column chromatography.[61]

Acidic hydrolysis of 1-acetyl-3-acetoxyazetine **38** afforded the parent azetidin-3-one hydrochloride **39**,[62] although other authors were not able to repeat this experiment and expressed doubt about the correctness of these data (Scheme 9).[24]

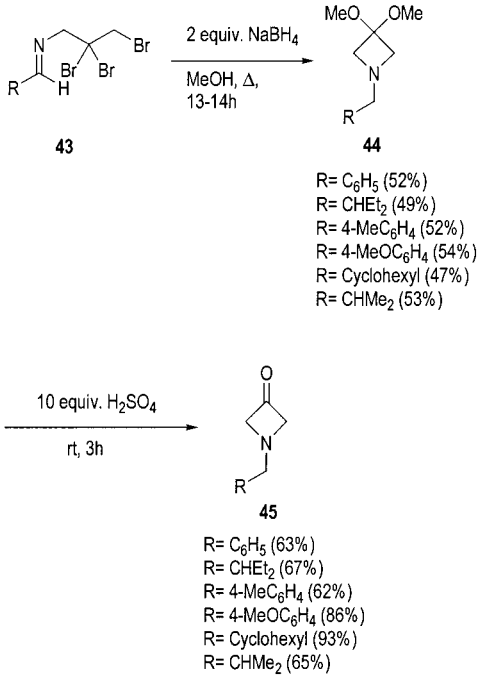
Scheme 9

Another elegant way for generating a ketone function is the hydrolysis of the corresponding acetal. Electroreduction of the aromatic imine **40** in the presence of chlorotrimethylsilane as a trapping agent of the anion intermediate resulted in ethyl 3-methoxy-2-phenyl-3-[(trimethylsilyl)oxy]-1-azetidinecarboxylate **41**, which was easily hydrolyzed to the corresponding 3-azetidinone **42** (Scheme 10).[63]

Scheme 10



Scheme 11



Also a new and straightforward synthesis of 2,4-unsubstituted 3-azetidinones is based on the hydrolysis of acetals **44**, obtained by cyclization of brominated aldimines **43** (Scheme 11).[64] The starting imines **43** are easily synthesized by reaction of 2,2,3-tribromopropylamine hydrobromide with the corresponding aldehydes. Subsequent treatment with sodium borohydride in methanol results in reduction of the imine, followed by intramolecular nucleophilic substitution to form 3,3-dimethoxyazetidines **44**, after methanolysis of the geminal dibromo functionality. The resulting 3,3-dimethoxyazetidines **44** were hydrolyzed by concentrated sulfuric acid, yielding 2,4-unsubstituted 3-azetidinones **45**.[64]

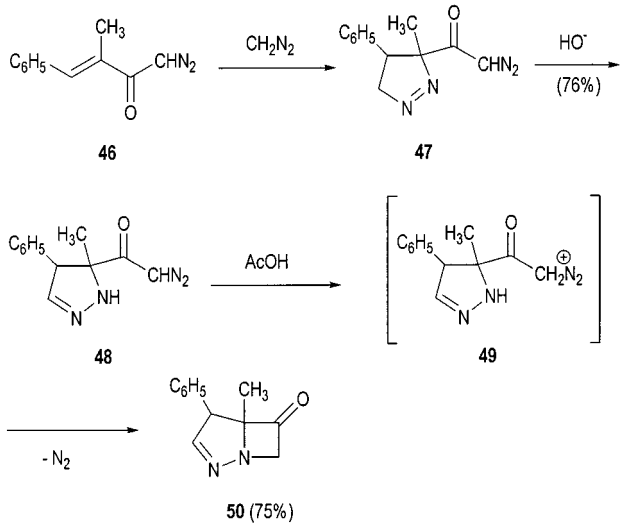
B.2. Intramolecular Cyclization Reactions

B.2a. Cyclization of α-Diazoketones. Despite apparent evidence of achievement of results in the synthesis of azetidin-3-ones with the use of oxidation methods of the corresponding alcohols, the bicyclic fused derivatives of azetidin-3-ones were obtained by cyclization reactions much earlier (Scheme 12). The first results on the cyclization of diazoacetylpyrazoline **48** into 1,2-diazabicyclo[3.2.0]hept-2-en-6-one **50** were published as early as 1959.[65]

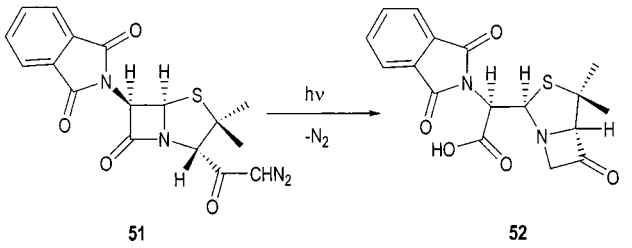
The cyclization of **48** proceeded in acidic medium in the presence of acetic acid. The basis of formation of the rather strained bicyclic four-membered structure can be explained by the high reactivity of the intermediate carbocation and the good leaving group capacities of molecular nitrogen.

The decomposition of diazo compounds was also initiated photochemically (Scheme 13). Thus, when penicillin-related systems were studied, 6β-phthalimidopenicillane diazoketone **51** was irradiated in a water−dioxane mixture, and the starting substrate concentration was monitored by the diazo group absorption in the IR spectrum at 2110 cm^{-1}, giving rise to the 6β-phthalimidohomopenicillanic acid **52**.[66,67]

Scheme 12

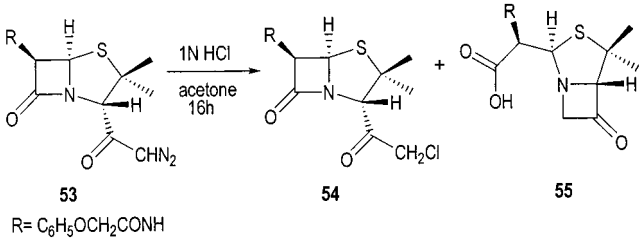


Scheme 13



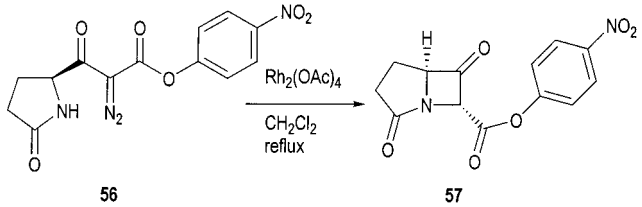
Contrary to 6β-phthalimido derivatives, which isomerized photochemically into compounds **52**, phenoxyacetamido derivatives of 6-aminopenicillanic acid **53** were transformed by treatment with 1 N hydrochloric acid into a mixture of the α-chloroketone **54** and the fused azetidin-3-one **55** (Scheme 14).[67]

Scheme 14



α-Diazoketone cyclization into bicyclic azetidin-3-ones proceeded also in a neutral solution in the presence of rhodium salts. This technique was used for the synthesis of some analogues of carbapenem acids, possessing antibiotic and antibacterial properties (Scheme 15).[68] A representative example con-

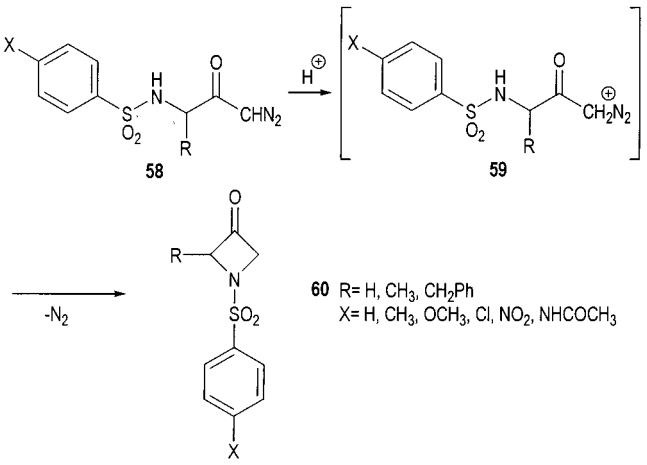
Scheme 15



cerns the conversion of α-diazoketone **56** into the 1-azabicyclo[3.2.0]heptane-2,6-dione **57**.

The synthesis of monocyclic azetidin-3-ones was accomplished by cyclization of α′-sulfamoyl-α-diazoketones **58** in acidic medium (Scheme 16).[25,69−71]

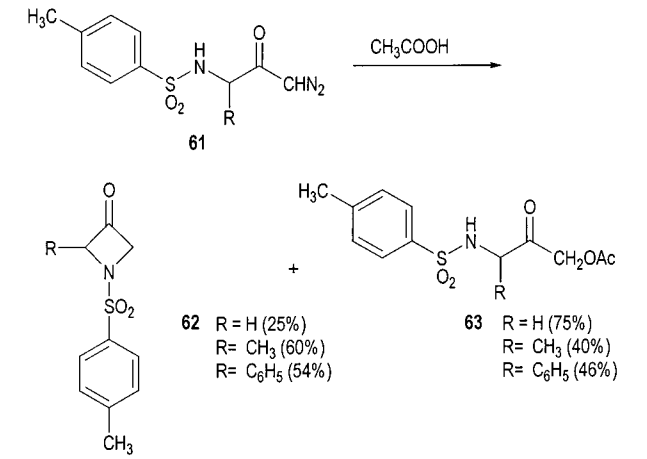
Scheme 16



For the decomposition of diazo compounds, inorganic acids or carboxylic acids were used. In the case of more nucleophilic agents (acetic acid, hydrochloric acid), linear products, such as α-acetoxymethyl ketones and α-chloromethyl ketones, were obtained. The ratio of azetidin-3-ones to acyclic products did not depend on the nature of the substituent on the benzene ring of the sulfamide. The yield of cyclization products increased in the presence of an alkyl or benzyl substituent on the α-position of the diazoketone.

The investigation of the acetolysis of α′-sulfamido-α-diazoketones **61** led to similar results (Scheme 17).[72] Also in this case, the presence of an additional

Scheme 17

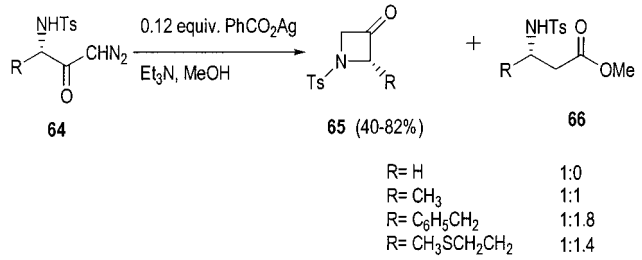


α′-substituent (R = CH_3, C_6H_5) seemed to be profitable for the cyclization toward azetidin-3-ones.

With decomposition of diazoketones in methylene chloride in the presence of catalytic copper bis(hexafluoroacetylacetonate), the yield of azetidin-3-ones **62** from α-diazoketones **61** rose from 25 to 60 to 80%.[72]

Application of Wolff rearrangement conditions, i.e., the use of silver benzoate dissolved in triethylamine as catalyst in methanol, to diazoketones derived from α-amino acids gave both normal Wolff rearrangement products **66** as the insertion products **65** (Scheme 18).[73] The different product ratios were explained by

Scheme 18

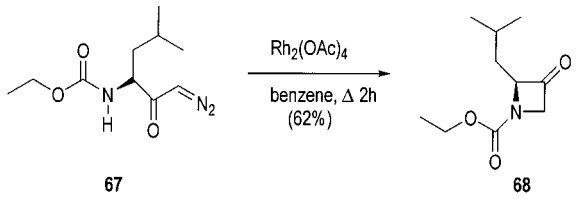


the different degree of steric hindrance of the side chain of the amino acid derivatives. Under these conditions, the possibility of a free carbene in the diazo decomposition was suggested.[73] In contrast to previous results (see Scheme 17), here, the additional substitution decreased the yield of azetidin-3-ones. Apparently, in these cases, the reaction pathway is directed by the conditions and reagents used to decompose the diazo compounds.

A similar case had already been described for the *N*-tosyl-L-alanine derived diazoketone under treatment with aqueous silver nitrate, resulting in the formation of the corresponding 3-azetidinone.[74]

The use of rhodium acetate in the decomposition of diazo compounds is widespread, which is also reflected in the synthesis of 3-azetidinones.[21,28,75,76,78] As an example, treatment of the diazo compound **67** with rhodium acetate in benzene gave the corresponding 3-azetidinone in 62% yield (Scheme 19).[75]

Scheme 19



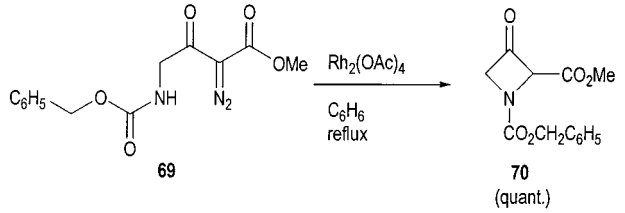
In this context, a new synthesis of α-amino-α′-diazomethyl ketones has been described very recently via ring opening of triethyl[(1-methoxy-2,2-dimethylcyclopropyl)oxy]silane upon treatment with various alkyl azides.[76] The resulting diazoketones were also converted in the corresponding 3-azetidinones.[76]

The use of copper(II) acetylacetonate in benzene has been reported to perform this intramolecular N−H insertion in a suitable way.[77]

The general approach for the synthesis of four-, five-, and six-membered nitrogen, oxygen, and sulfur heterocycloalkanones, based on rhodium catalyzed intramolecular cyclization reactions of α-diazo-*β*-ketoesters, was applied to α-diazo-α′-aminoketones **69** to give access to 3-oxoazetidin-2-carboxylic esters **70** in quantitative yields (Scheme 20).[78]

The cyclization of α-amino-α′-diazomethyl ketones has also been reported to occur in the ion source of a mass spectrometer. This method has been elaborated for electron impact ionization and chemical ionization and can potentially be used to predict the direction

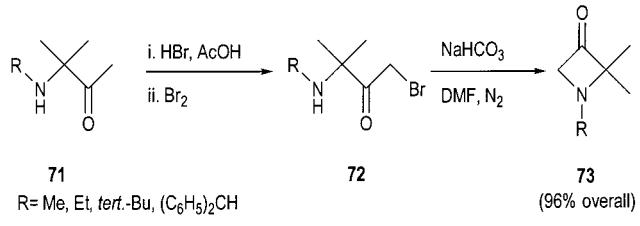
Scheme 20



and yield in the acid-catalyzed cyclization of diazoketones in solution.[79]

B.2b. Cyclization of α-Amino-α′-Halomethyl ketones and α′-Amino-α,*β*-Epoxyketones. There are only a few examples of the use of intramolecular cyclization reactions for the synthesis of azetidin-3-ones from α-amino-α′-haloketones. The successful cyclization of *N*-substituted 3-amino-3,3-dimethyl-1-bromobutan-2-ones **72** to 2,2-dimethylazetidin-3-ones **73** was probably caused by the presence of geminal dimethyl groups, promoting the formation of the strained ring by the Thorpe-Ingold effect (Scheme 21).[80−83]

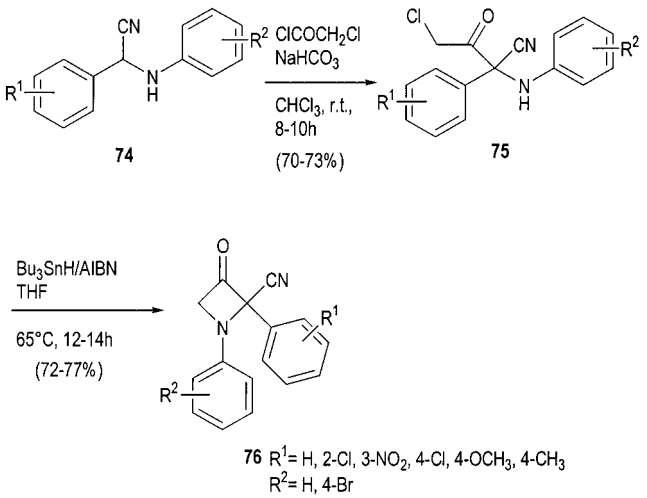
Scheme 21



This same cyclization method has been applied in the synthesis of 7-azetidinylquinolones, possessing antibacterial activity.[84] It was found that some azetidin-3-ones possess hypotensive activity, and azetidin-3-ols obtained from them (by reduction with $NaBH_4$ or reaction with PhLi) are central nervous system stimulators.[84]

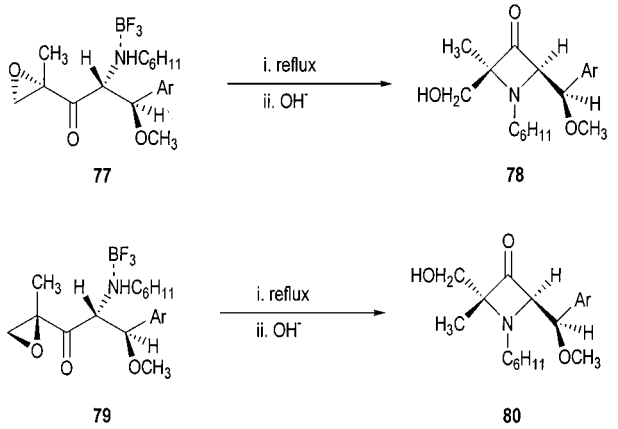
Also a tri-*n*-butyltinhydride/azoisobutyronitrile-induced radical intramolecular ring closure of α′-anilino-α-(chloromethylcarbonyl)phenylacetonitriles **75** yielding 1,2-diaryl-2-cyanoazetidin-3-ones **76** in 72−77% yield has been reported (Scheme 22).[85]

Scheme 22



It is known that the oxirane ring is an effective acceptor of nucleophilic functional groups in reactions of intramolecular cyclizations. In this connection, epihalohydrines are widely used in the synthesis of azetidin-3-ols. It was expected that the cyclization of α′-amino-α,*β*-epoxyketones will not proceed so unambiguously, in view of the possibility of four- and five-membered ring formation, and also due to the smaller conformational flexibility (less number of conformations favorable for cyclization are formed) of the carbonyl substrate (Scheme 23). The synthesis

Scheme 23



of functionalized azetidin-3-ones **78**, **80** was accomplished by cyclization of α′-amino-α,*β*-epoxyketones **77**, **79** complexed with boron trifluoride, in aprotic polar solvents.[27,86−89] It was established that the heterocyclization proceeded stereospecifically, which was confirmed by transformation of both diastereomers with the erythro-configuration into the corresponding stereoisomeric 4-(arylmethoxymethyl)-2-hydroxymethyl-2-methyl-1-cyclohexylazetidin-3-ones.

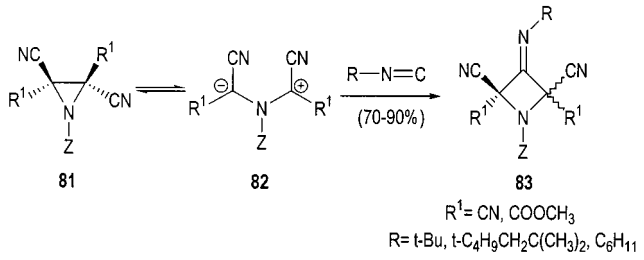
The mechanism of the formation of these compounds includes dissociation of the boron trifluoride complexes with recoordination of boron trifluoride from the nitrogen atom to the oxygen atom of the oxirane ring with subsequent intramolecular exo-attack of the amino group at the destabilized α-C−O bond of the oxonium complex. Formally, the process can be considered as an intramolecular nucleophilic substitution of the oxirane oxygen atom by the amino group.[88]

B.3. 1,3-Dipolar Cycloaddition Reactions

Formally, the azetidin-3-one skeleton can be constructed by cycloaddition of an azomethine ylide with carbon monoxide. However, in the literature there are no data about the implementation of such possibility. There are nevertheless three reports about the [3+1]-cycloaddition of azomethine ylides, generated from aziridines or 1,2,3-triazolines to isonitriles (Scheme 24).[90−92] Reaction of aziridines **81** with isocyanides afforded two diastereomeric azetidines **83**, which did not undergo epimerization in $CDCl_3$ solution.

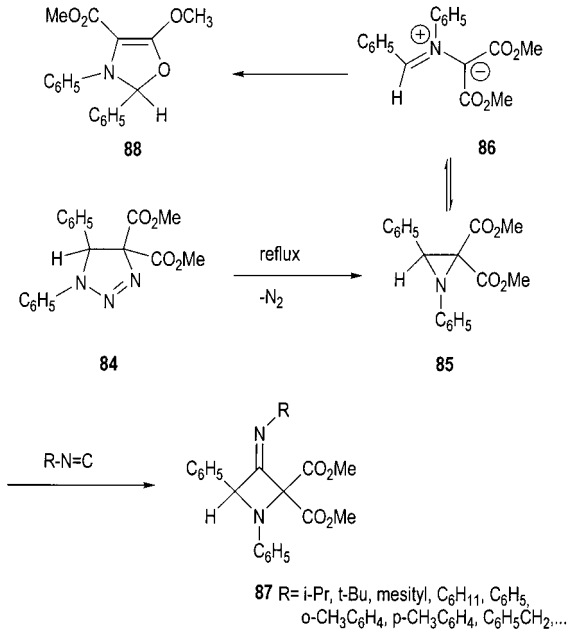
Oxazolines **88** were not formed as a byproduct in this reaction in contrast to the case of unsymmetri-

Scheme 24



cally substituted azomethine ylides, generated from 1,2,3-triazolines **84** (Scheme 25).[92]

Scheme 25



In these papers,[90−92] the mechanism of cycloaddition and formation of cyclic and acyclic products was discussed in details, but there were no data available on the hydrolysis of 3-iminoazetidines **83**, **87** into azetidin-3-ones.

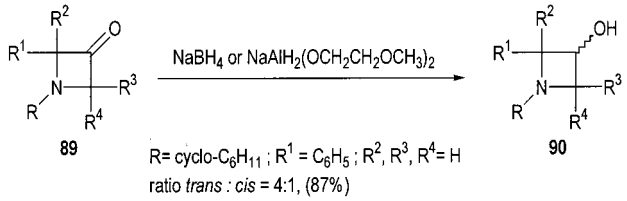
C. Chemical Properties of Azetidin-3-ones

Chemical properties of azetidin-3-ones, which are not substituted with functional groups, are determined by the presence of the carbonyl group and the nitrogen atom in the ring, providing the usual properties of ketones and amines. The presence of an additional functionality in the molecule gives the possibility of reactions with involvement of other substituents present in the molecule, and also of reactions with ring extension.

C.1. Transformations of the Carbonyl Group

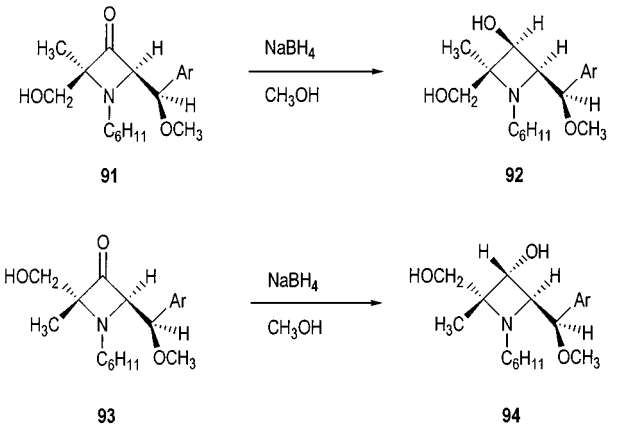
Nucleophilic addition reactions across the carbonyl group of azetidin-3-ones were investigated most thoroughly. Reduction of unsubstituted and 2,4-substituted azetidin-3-ones by complex metal hydrides resulted in azetidin-3-ols **90** with a preferential *trans*-configuration of the substituents (Scheme 26).[28,31,38,40,93]

Scheme 26



The reduction of 4-(arylmethoxymethyl)-2-hydroxymethyl-2-methyl-1-cyclohexylazetidin-3-ones **91**, **93** with sodium borohydride led to the stereospecific formation of the corresponding azetidin-3-ols **92**, **94** (Scheme 27).[88] Probably, coordination of the reducing

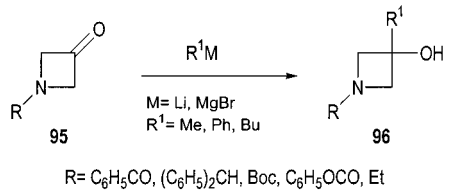
Scheme 27



agent with the hydroxy-function blocked the corresponding face of the molecule, leading to hydride attack from the opposite face.

The addition of organometallic reagents, e.g., organolithium and organomagnesium derivatives, to azetidin-3-ones **95** resulted in the formation of tertiary alcohols **96** (Scheme 28),[28,38,40,81,64,94,96] which

Scheme 28

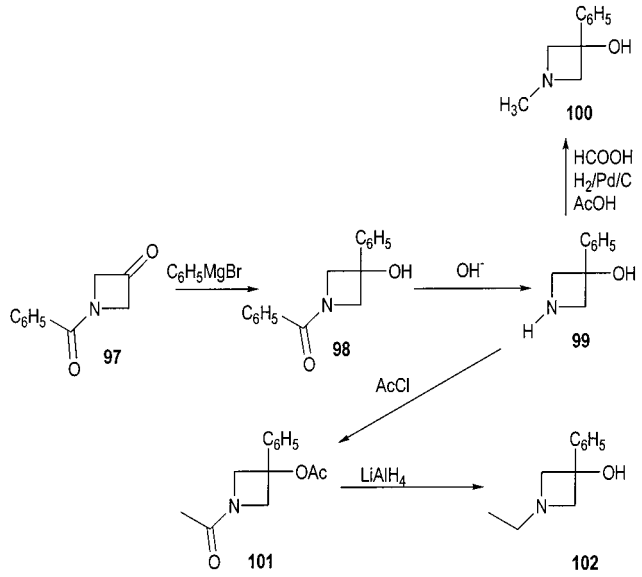


display some biological activity, e.g., analgesic activity.[41,42] Most of these results were obtained with electron-withdrawing or bulky substituents on the ring nitrogen atom. Attempts to dehydrate the azetidin-3-ols thus obtained failed.[38]

Addition of methylmagnesium bromide to *N*-diphenylmethylazetidin-3-one, followed by a Ritter type reaction on the azetidin-3-ol, has been described in very low yield.[95] This low yield was explained by stablization of the intermediate carbocation by the ring nitrogen atom, allowing side reactions to occur.[95]

With the purpose to have a possibility of variation of substituents at the nitrogen atom, *N*-benzoylazetidin-3-ones can be introduced in this reaction, with consequent removal of the benzoyl group and further chemical transformations (Scheme 29).[41] In this perspective, also 1-benzhydryl-azetidin-3-one hydro-

Scheme 29

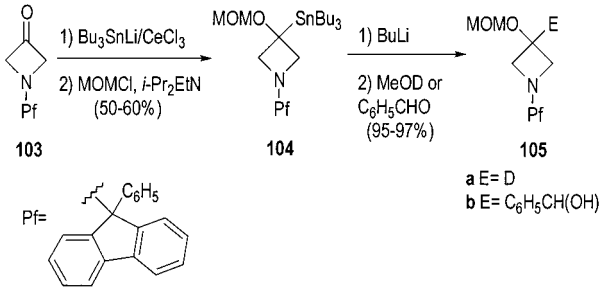


chlorides have been used. Hydrogenolysis with Pd-$(OH)_2$ as catalyst under 60 psi H_2 gave the *N*-unsubstituted azetidin-3-one hydrochloride that could be further modified at nitrogen.[24,57]

Direct treatment of 1-benzhydryl-3-azetidinones with excess methyl or ethyl chloroformate also afforded the corresponding 1-alkoxycarbonyl-3-azetidinones in quantitative yields.[24,96]

Very recently, 1-(9-phenylfluorene-9-yl)-3-azetidinone **103** was converted to the corresponding MOM-protected stannyl alcohol **104** by sequential reaction with $Bu_3SnLi/CeCl_3$, followed by MOMCl/DIPEA.[97] The latter α-alkoxy-*β*-aminostannane **104** was used to investigate the synthesis and stability of the corresponding organolithium compound after tin−lithium exchange. The tin−lithium exchange was confirmed after quenching experiments with different electrophiles, e.g., D_2O and benzaldehyde (Scheme 30).[97] Furthermore, the stability of the intermediate

Scheme 30

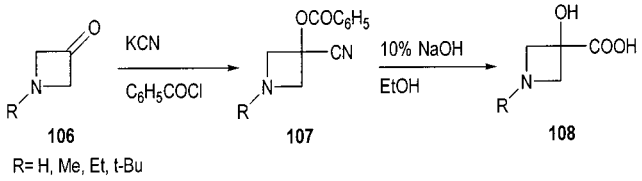


organolithium compounds decreased with ring size of the azaheterocycle (the corresponding pyrrolidines and piperidines were included in this study), resulting in the formation of ring-opened alkenes.[97]

A lot of typical reactions for the carbonyl group have also been performed on azetidin-3-ones. A short, but comprehensive, overview of these transformations is given in the remaining part of this chapter.

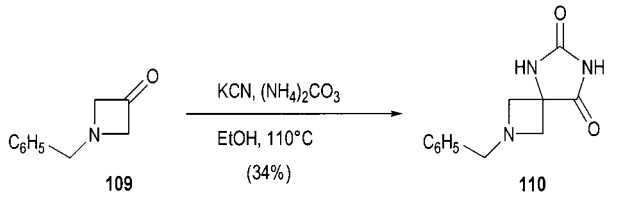
The reaction of potassium cyanide with 1-substituted azetidin-3-ones **106** in the presence of benzoyl chloride led to the formation of the cyanohydrine benzoate **107**, giving 3-hydroxyazetidin-3-carboxylic acids **108** after hydrolysis (Scheme 31).[31,38,80]

Scheme 31



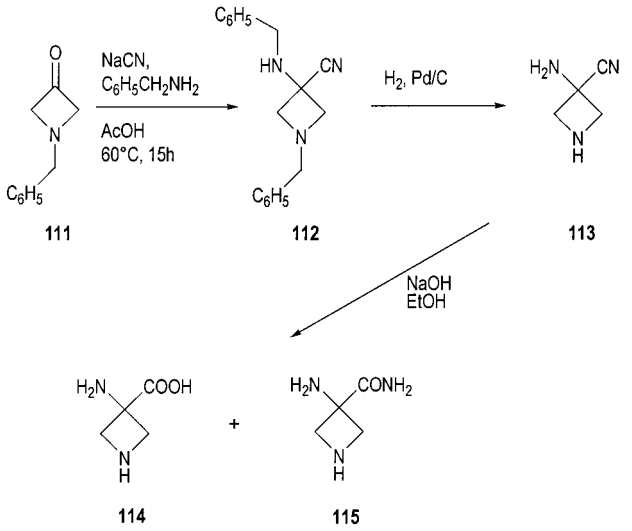
Heating of 1-benzylazetidin-3-one **109** with potassium cyanide and ammonium carbonate in ethanol gave rise to the formation of the spirohydantoin **110**, the classical precursor to the corresponding α-amino acids (Scheme 32).[40]

Scheme 32



Reaction of 1-benzylazetidin-3-one **111** with sodium cyanide and benzylamine gave 3-benzylamino-3-cyanoazetidine **112** (Scheme 33). Further double

Scheme 33



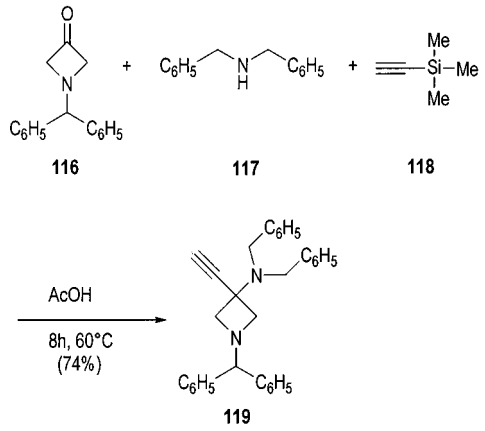
N-debenzylation and reaction with sodium hydroxide yielded the corresponding α-amino acid **114** or its amide **115**.[44]

The formation of 1-benzhydryl-*N*,*N*-dibenzylamino-3-ethynyl-3-azetidine **119** was obtained upon treatment of 1-benzhydryl-3-azetidinone **116** with dibenzylamine and ethynyl(trimethyl)silane in the presence of acetic acid (Scheme 34).[98]

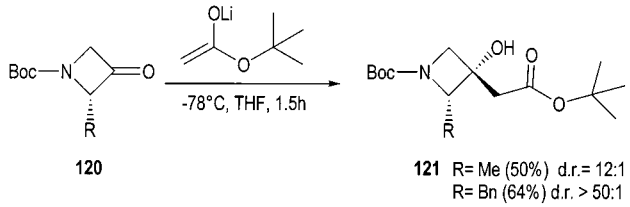
The reaction of the chiral azetidin-3-ones **120** with the lithium enolate of *tert*-butyl acetate led to the corresponding *γ*-amino-*β*-hydroxyester derivatives **121** in excellent diastereoselectivities (Scheme 35).[28]

Azetidin-3-ones easily form oximes, hydrazones, and azines, which have found an application in the

Scheme 34



Scheme 35



synthesis of other azetidine derivatives (Scheme 36).[40,47,52,57,58,99] Examples in this respect concern the synthesis of compounds **123** and **129**. Also a Wolff−Kishner reduction of an azetidin-3-one has been performed (**124** → **125**).[50] Further reduction and catalytic hydrogenolysis yielded compound **127**.

Thiadiazoline **131** was formed upon reaction of azine **129** with dihydrogen sulfide and subsequent oxidation of the thiadiazolidine with DEAD. Reflux of thiadiazoline **131** in toluene resulted in the loss of molecular nitrogen, while subsequent desulfurization of the bisspiro compound **132** by treatment with triphenylphosphine gave rise to the alkylidene(bis)-azetidine **133**.[99]

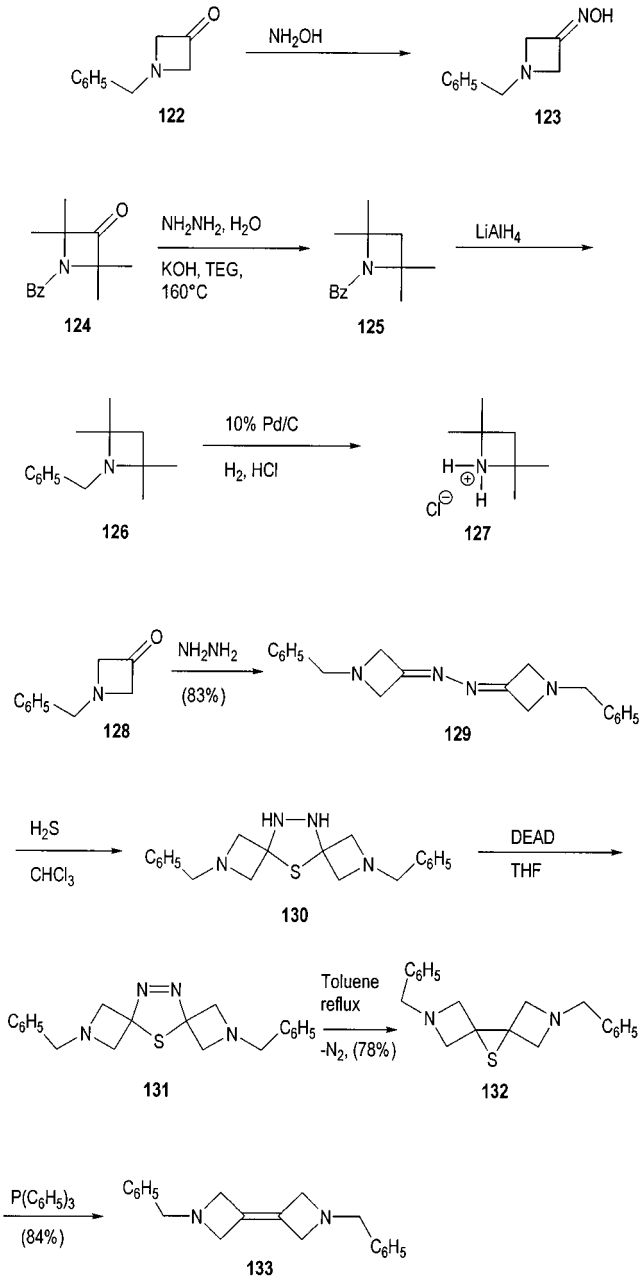
Condensation of azetidin-3-ones with Wittig−Horner reagents led to the corresponding methylene derivatives **135** and **136** in yields of 25−92% (Scheme 37).[18,20,24,40,55,100]

The reaction of azetidin-3-ones **137** with [(methoxycarbonyl)-methylidene]-triphenylphosphorane at elevated temperature afforded the unsaturated amino acid derivative **138** (Scheme 38). Although decreasing diastereoselectivity, reaction at elevated temperatures was needed since it was observed that the formation of the strained C=C bond took a higher than usual activation energy.[28] Hydrogenation of the C−C double bond gave the saturated ester **139** in a diastereomeric ratio of 1.4:1.[28]

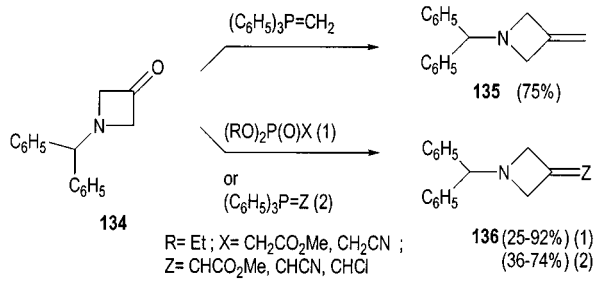
N-(Trifluoromethanesulfonyl)-3-(dibromomethylidene)azetidine was obtained from the reaction of the corresponding azetidin-3-one, carbon tetrabromide, and triphenylphosphine in toluene.[53]

Azetidin-3-ones were used as starting materials for the generation of *N*-substituted-3-azetidinylidene carbenes **141** (Scheme 39). The reactive intermediates produced via base-promoted reactions of *N*-tosyl- and *N*-benzhydrylazetidin-3-ones with diethyldiazomethylphosphinate (DAMP) have been shown to be

Scheme 36



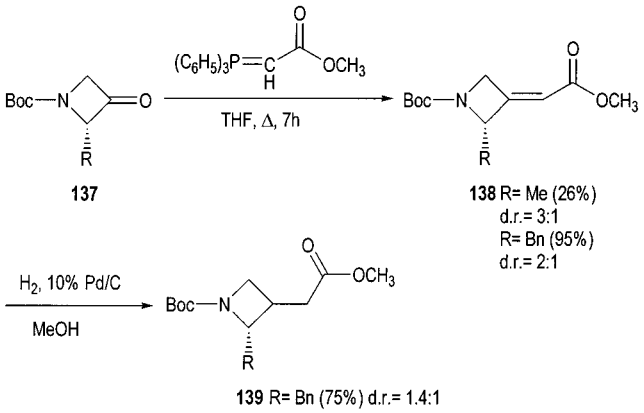
Scheme 37



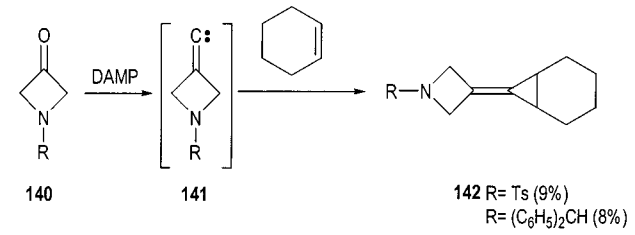
vinylidenecarbenes rather than the corresponding cycloalkynes. Thus, *N*-tosylazetidin-3-ylcarbene **141** was trapped in situ by cyclohexene to afford a cycloadduct, i.e., 1-*p*-toluenesulfonyl-3-(7′-bicyclo-[4.1.0]heptanylidene)azetidine **142**.[101]

From these examples, it can be seen that azetidin-3-ones can serve as useful intermediates in the

Scheme 38



Scheme 39



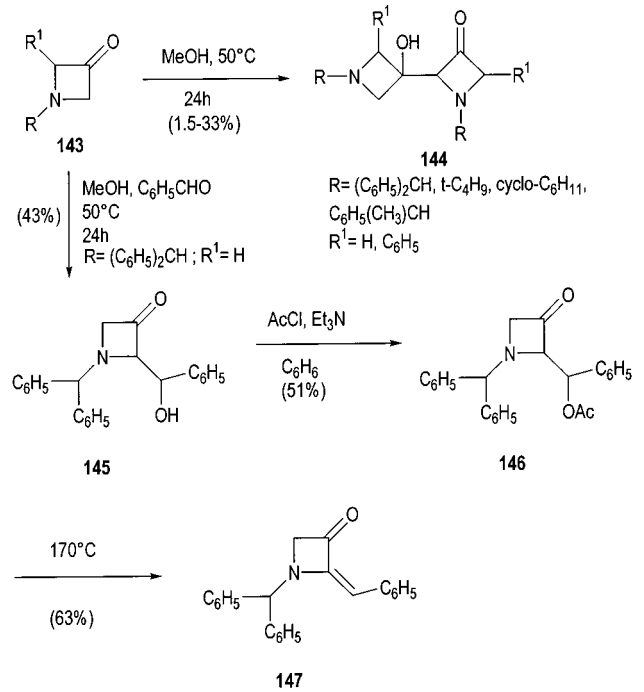
synthesis of more functionalized azetidines that are difficult to obtain otherwise.

C.2. Condensation Reactions – Synthesis of 2-Benzylideneazetidin-3-ones

The reactions of azetidin-3-ones with involvement of the α-carbon atoms are illustrated in the literature by one example, the aldol condensation (Scheme 40).

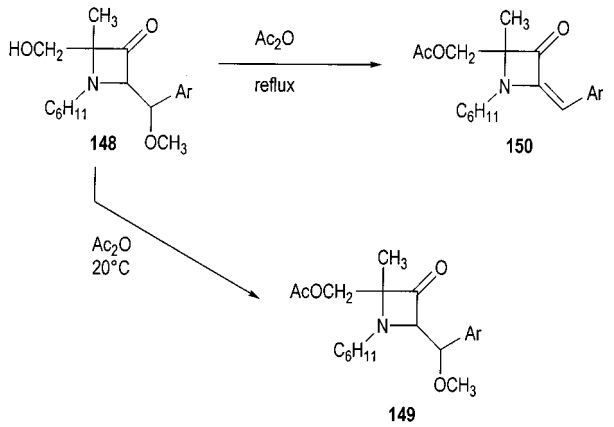
Azetidin-3-ones **143** are unstable compounds at elevated temperature as they give rise to self-condensation. This aldol-type condensation of **143** to **144** ran smoothly in methanol at 50 °C.[40] In the presence of benzaldehyde, azetidin-3-ones **143** afforded the aldol product **145**, which could be acylated, the latter gave rise to elimination of acetic acid under thermal conditions, providing 2-benzylideneazetidin-3-ones **147**.[40] The aldol products **145** proved to be rather stable compounds, which only gave elimination upon more stringent reaction conditions.

Scheme 40



Alternatively, 2-benzylideneazetidin-3-ones **150** were obtained also from 4-(arylmethoxymethyl)-2-hydroxymethyl-2-methyl-1-cyclohexyl-azetidin-3-ones **148** by reaction with acetic anhydride (Scheme 41).[71] Depending on the acetylation conditions, either the corresponding acetates **149** or 4-arylidene-2-acetoxymethyl-2-methyl-1-cyclohexylazetidin-3-ones **150** were produced.[88]

Scheme 41

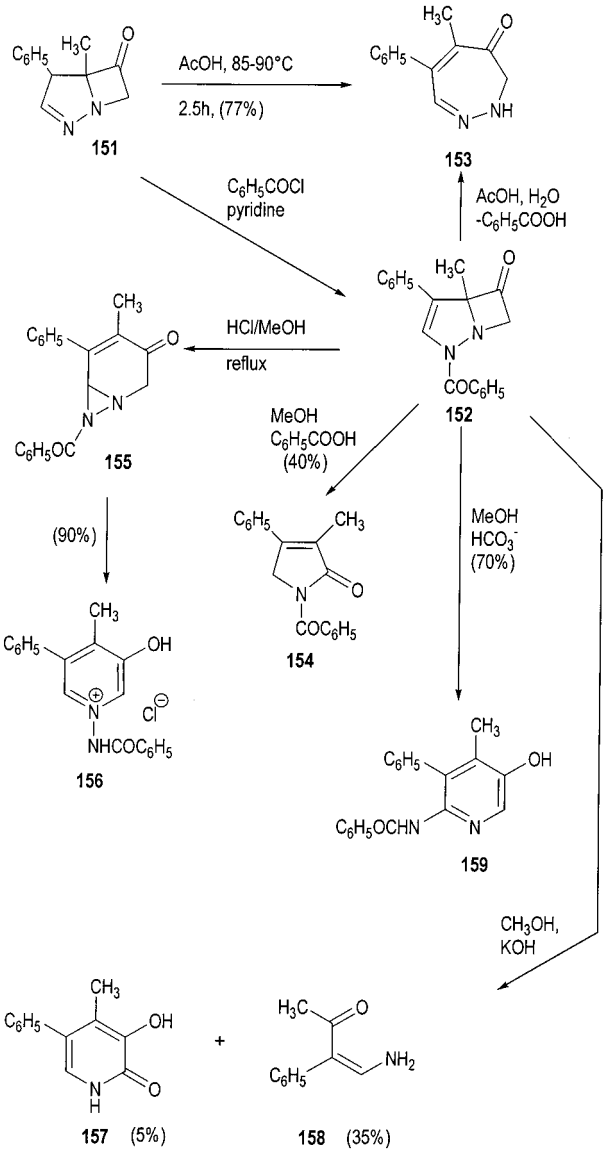


C.3. Ring Transformations of Azetidin-3-ones

The chemical transformations of bicyclic fused azetidin-3-ones **151** are distinguished by a diversity of reactions (Scheme 42).[65,102,103]

Benzoylation of the bicyclic ketone **151** afforded 2-benzoyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one **152**. Further reaction of the latter compound with a warm glacial acetic acid solution yielded the diazepinone **153**. Reflux of **152** in methanol (containing benzoic acid and sodium benzoate) gave the 1-benzoylpyrrolone **154**. Alkaline methanolysis (catalytic amount of ammonia or bicarbonate) produced as the major product 6-benzamido-3-hydroxypyridine **159**. Performing the reaction in methanol without added reagents gave compound **154** as well as compound **159**. The reaction products were believed to result from the same precursor, obtained by concerted rupture of the N−N and C5−N bond. Recyclization via two different ways resulted in the two isolated compounds. The bicyclic system of compound **152** rearranged to 1-benzamidopyridinium chloride **156** upon treatment with an aqueous methanolic hydrochloric acid solution. This reaction consists of an allylic shift of the bridging bond from C5 to C3, followed by decomposition of the bicyclic intermediate **155**. Finally, treatment of **152** with cold methanolic potassium hydroxide afforded a mixture of lactam **157** and enaminone **158**. A common precursor for the formation of these compounds resulted from deprotonation at the azetidin-3-one moiety, followed by cleavage of the N−N bond and hydrolysis.

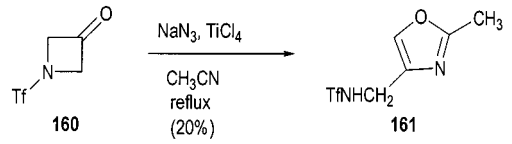
Scheme 42



The rich synthetic potential of these bicyclic compounds **152** in the described transformations can be explained by involvement of the azetidin-3-one fragment.

Monocyclic azetidin-3-ones undergo ring expansion as well. For instance, prolonged reflux of a mixture of *N*-triflylazetidin-3-one **160**, sodium azide, and titanium(IV) chloride in acetonitrile afforded the substituted oxazole **161** in a yield of 20% and the starting unreacted **160** in 25% yield (Scheme 43).[104]

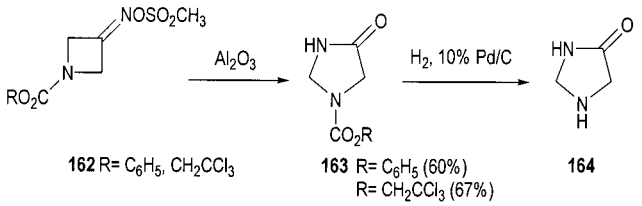
Scheme 43



At present, the mechanism of this reaction is not yet fully understood. A control experiment was performed by treating azetidin-one **160** with titanium(IV) chloride in acetonitrile in the absence of sodium azide. In this case, the oxazole **161** was not detected. The only conclusion so far is that sodium azide must actively participate in the mechanism for the conversion of **160** into **161**.

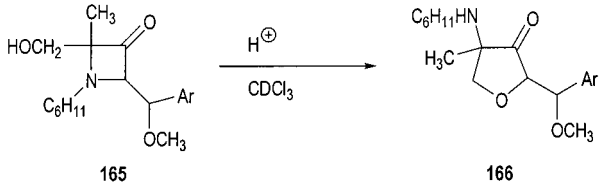
The first synthesis of imidazolidin-4-ones **164** by Beckmann rearrangement of *N*-mesyl-1-alkoxycarbonylazetidin-3-one oxime **162** on alumina was carried out (Scheme 44).[96] Standard reagents for Beckmann rearrangement, such as polyphosphoric acid, sulfuric acid, and formic acid, failed in this particular case. Attempts to synthesize **164** directly from the *N*-ethoxycarbonyl-azetidin-3-one by a Schmidt type reaction was unsuccessful and led only to acyclic products.[96]

Scheme 44



2-(Hydroxymethyl)azetidin-3-ones **165** rearranged in acidic medium to give rise to tetrahydrofuran-3-ones **166** (Scheme 45).[105]

Scheme 45

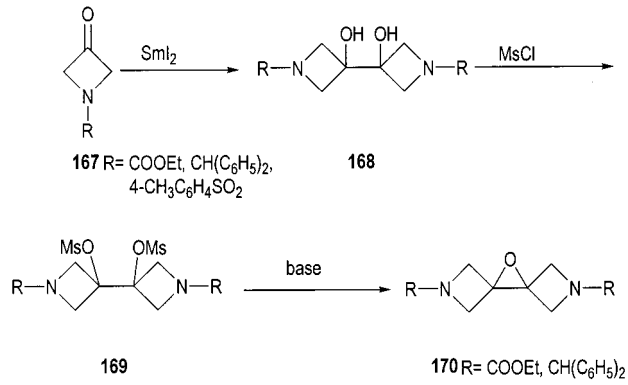


These ring transformations reflect the possibilities of the azetidin-3-one ring toward ring expansion, due to the reactive N−CH_2−CO moiety in this strained ring system.

C.4. Miscellaneous

Samarium iodide promoted reductive coupling of compounds **167** afforded the corresponding pinacol derivatives **168** (Scheme 46). After conversion into

Scheme 46

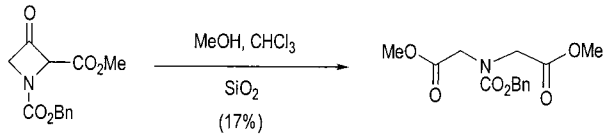


the dimesylate **169** and heating in the presence of base, the corresponding spirocyclic oxiranes **170** were

obtained. Only *N*-*p*-toluenesulfonyl protected azetidin-3-ones seemed to be inert under these conditions.[106]

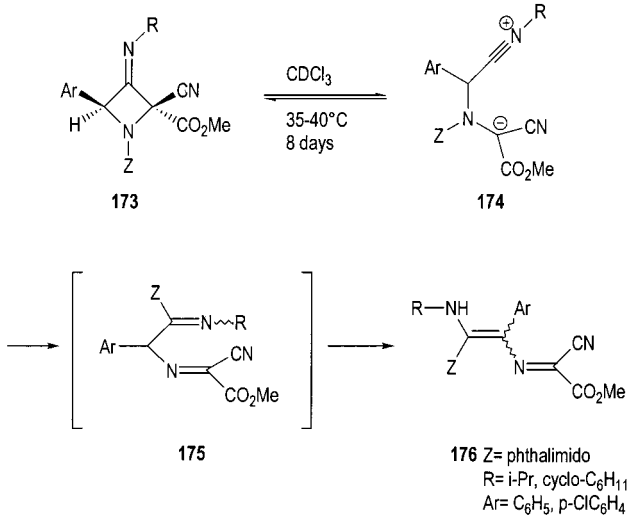
Acid-catalyzed ring opening of azetidin-3-ones **171** has been observed during silica gel chromatography, using methanol as the eluent (Scheme 47).[78] The

Scheme 47

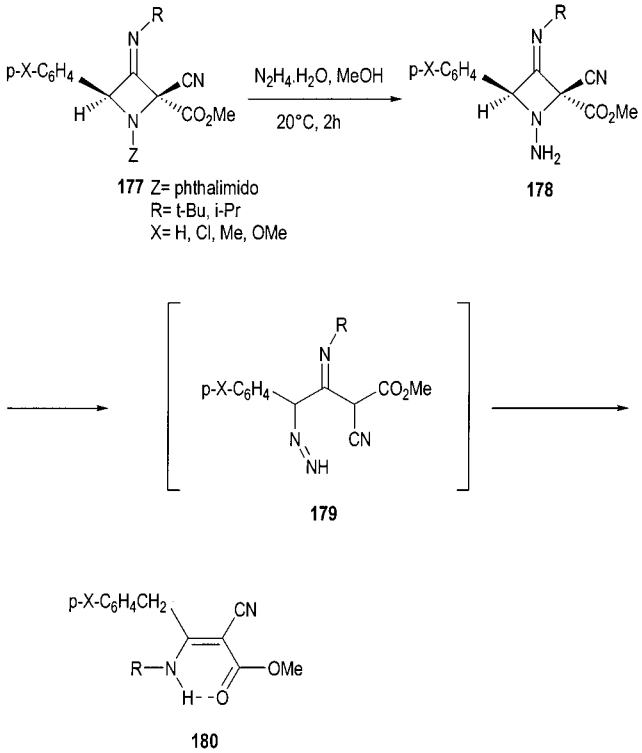


extreme lability of this heterocycle toward nucleophilic ring opening originates from the ready cleavage of the β-ketoester moiety according to a retro-Claisen reaction.

Scheme 48



Scheme 49



The involvement of the azetidine ring in 3-iminoazetidine **173** did not necessarily lead to ring expansion but also produced acyclic unsaturated products, as exemplified for the conversion of **173** into functionalized 2-azabutadienes **176** (Scheme 48).[90,91]

These 3-iminoazetidines **177** were also cleaved with hydrazine hydrate at room temperature, forming enaminoesters **180** (Scheme 49).[91]

Considering the reactions, presented in the given review, it is clear that the methods for azetidin-3-one synthesis are not exhausted. New research will undoubtedly result in the creation of new approaches to azetidin-3-ones. The full extent of their synthetic potential remains to be discovered.

III. The Chemistry of Oxetan-3-ones

Unlike azetidin-3-ones, oxetan-3-ones **181** have been scarcely cited in the literature (Figure 4). Rather

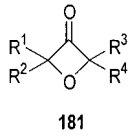


Figure 4.

few examples are known, and also their chemistry is quite unknown. Unsubstituted oxetan-3-one **181** itself was first isolated and characterized as its 2,4-dinitrophenylhydrazone derivative, as late as 1952.[107] Only in 1967, oxetan-3-one **181** (R^1, R^2, R^3, R^4 = H) was isolated in pure state and characterized unambiguously.[108] Before, some inadvertent preparations of substituted oxetan-3-ones were published and verified later.[110−113]

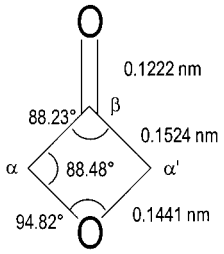
Oxetan-3-ones are not yet found in nature, and data about their biological activity are very rare. An exception on this last point concerns a series of steroids that contain the oxetan-3-one substructure.[114−118] Described biological activities of these steroidal oxetan-3-ones include antiinflammatory activity[114] and antiglucocorticoid activity,[117] while some of them act as oral diuretics.[118] Other applications of oxetan-3-ones involve the use as solvent, especially for the synthesis of cyanoethyl cellulose in the preparation of binders for electroluminescent panels.[108,109]

The further chapter will be divided in an analogous way as the one for the azetidin-3-ones, i.e., treating structural data, synthetic ways to oxetan-3-ones, and finally further transformations successively.

A. Structural Data

The structure and electronic properties of the parent unsubstituted oxetan-3-one **181** have been studied extensively by a wide range of different techniques.[119−129] Photoelectron spectroscopy was used to determine the electronic structure of the strained ring system, more specifically the possibility of the nonbonding oxygen orbital for interaction (through space and/or through bond) with the exocyclic π−orbital.[119] Inspection of the eigenvectors resulting from the molecular orbital calculation methods (MINDO/3, MNDO, STO-3G) leaves no

doubt that the interaction is primarily a through-bond rather than a through-space interaction.[119,120,121] The STO-3G calculation method was also applied to thietan-3-one.[121] These calculations also show considerable electrondensity on the pseudo πCH_2-orbitals.[119] Microwave spectrum techniques, infrared spectrum techniques, and ab initio calculations by the force method have been applied to determine the structure of the ring, i.e., the planarity or nonplanarity of the ring.[122−126] Molecular mechanics calculations (MM2) were utilized to estimate the barriers to planarity in some small ring molecules, including oxetan-3-one.[127] The effect of carbonyl substitution on ring planarity and ring-puckering vibration was analyzed for oxetanes and thietanes.[128] In addition to the contributions of ring angle deformation and unstrained torsions about the ring bonds, the model for this calculation also included a torsional strain parameter.[128] These studies led to the conclusion that the oxetan-3-one ring has a planar equilibrium configuration.[122,125] Using the same technique, expanded with some calculations of moment equations and isotopic substitution experiments, a proposal was reached concerning bond lengths and bond angles in oxetan-3-ones (Figure 5).[122]



182

Figure 5.

In addition, vibrational model studies revealed that the ring bends more about the $C_\alpha-C_{\alpha'}$ diagonal than the $C_\beta-O$ diagonal during vibration.[122−124] An explanation for this phenomenon is found in considering the relative amounts of strain present for the internal ring angles.[122] The central C-atom in the $C_\alpha-C_\beta-C_{\alpha'}$ angle has a nominal sp^2-hybridization, resulting in a 120° equilibrium angle. Thus, this angle is more highly strained and resists to further motion of the ring which causes further bending. This fact maximizes bending about the $C_\alpha-C_{\alpha'}$ diagonal which involves no change in the $C_\alpha-C_\beta-C_{\alpha'}$ angle. Torsional forces also favor the planar configuration in oxetan-3-one **182**, presumably because there are no adjacent methylene hydrogens.[122,128] The molecular Zeeman effect and other magnetic parameters of oxetan-3-one were measured.[129] Also, the crystal and molecular solid-state structure of a carbohydrate-derived oxetan-3-one has been described (vide infra).[130] X-ray analysis shows that the monosubstituted oxetan-3-one has an almost planar configuration (the ring oxygen being out of the C−C(O)−C plane by 0.10 Å), and values for bond lengths and bond angles of the oxetan-3-one are in the same order of magnitude as the ones already mentioned.

IR-carbonyl absorptions in the range of 1802−1820 cm^{-1} are characteristic for oxetan-3-ones.[131−133] Oxetan-3-ones also exhibit an additional strong ring absorption at ca. 900 cm^{-1}.[121]

^1H NMR studies report a deshielding of the α-protons to the carbonyl group, appearing at a δ-value of 5.6 ppm (100 MHz, $CDCl_3$).[130] The NMR spectra of monosubstitute oxetan-3-ones show geminal coupling constants of 14.5−15.3 Hz for the oxetane ring methylene protons.[134] In the same case, long-range coupling constants between the ring methine proton and the ring methylene protons have been assigned 0−1.5 Hz (trans) and 3.5−4.0 Hz (cis).[134]

The mass spectra of oxetan-3-ones have not been thoroughly studied. However, molecular ions have been reported in most cases and in one case, the mass spectral decomposition of a steroidal oxetan-3-one showed clearly the loss of the elements of carbon monoxide.[116]

Oxetan-3-one **181** (R^1, R^2, R^3, R^4 = H) is unstable in the presence of base and slowly polymerizes on standing, giving a highly viscous material, possibly polyoxetanone [-$CH_2C(O)$-CH_2O-].[136]

B. Synthetic Methods for Oxetan-3-ones

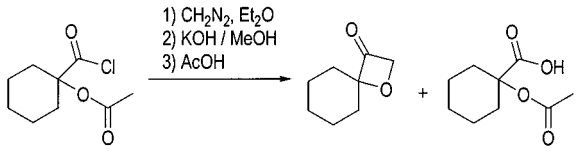
The synthetic methods for oxetan-3-ones can be grouped as follows:

1. Decomposition of Diazoketones
2. Oxidation Reactions
3. Intramolecular Displacement Reactions
4. Miscellaneous

B.1. Decomposition of Diazoketones

The first synthesis of substituted oxetan-3-ones was achieved by an acid-catalyzed decomposition of a diazoketone. 1-Acetoxycyclohexanecarbonyl chloride **183** was first reacted with diazomethane to afford the corresponding α-diazoketone, which subsequently reacted with base and acid to provide 1-oxaspiro[3.5]nonan-3-one **184** in 49% yield and 1-acetoxycyclohexane carboxylic acid **185**, as a minor reaction product after acidic workup (Scheme 50).[107]

Scheme 50

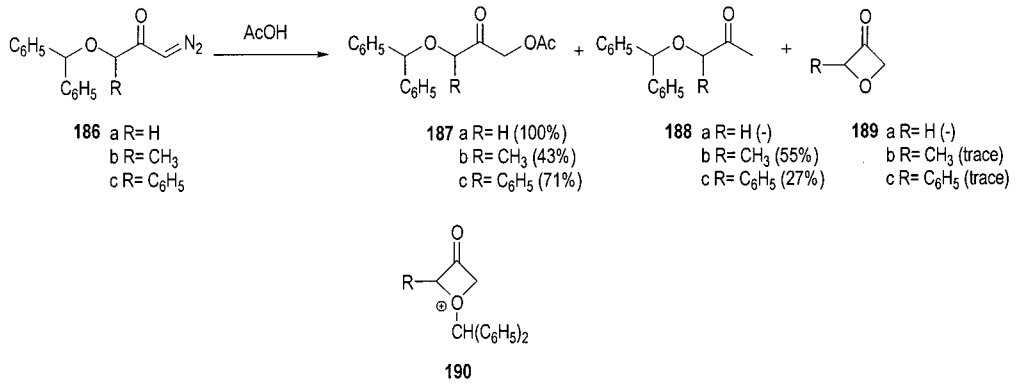


183 **184** (49%) **185** (minor)

The cyclization to the oxetan-3-one **184** was probably the result of acidolysis, since gas evolution was only observed at the third step.[130]

In main lines, the same strategy was applied to the synthesis of the parent oxetan-3-one itself. Chloroacetyl chloride was treated with diazomethane, followed by potassium carbonate in aqueous methanol.[107] The resulting oxetan-3-one was isolated as its 2,4-dinitrophenylhydrazone derivative in only low yield.[107] Acetolysis of the diazoketone **186** was conducted to determine neighboring group participation in the solvolysis or whether normal substitution proceeds through an intermediate oxonium ion.[137] The acetolysis of **186a** led exclusively to the α-ac-

Scheme 51

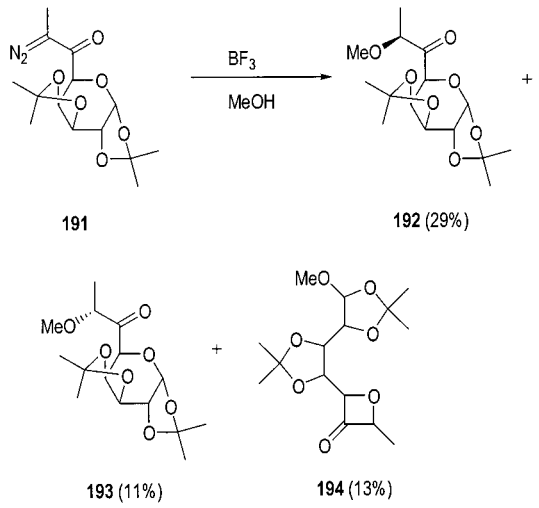


etoxyketone **187a**, which proved that an intermediate oxonium ion is not involved (Scheme 51).

However, in the case of **185b**,**c** the formation of α-(diphenylmethyl)ketones **188** and the corresponding oxetan-3-ones **187** involved clearly an oxonium ion intermediate **190**.[137] Since the ring-opened products at the R-substituted carbon atom were not detected, normal substitution seemed to proceed via an open chain mechanism.

Not only organic acids have been used in the decomposition of diazoketones, also boron trifluoride-catalyzed reactions have been described.[130] The first carbohydrate derived oxetane-3-one **194** was obtained by boron trifluoride-catalyzed methanolysis of the sugar-derived diazoketone **191** (Scheme 52).[130,138,139]

Scheme 52



The reaction mechanism was thoroughly investigated since the formation of the oxetan-3-one **194** implied the formation of the four-membered ring by opening of a six-membered ring and participation of the ring oxygen atom of a pyranose sugar.[130]

Boron trifluoride-catalyzed decomposition of compounds **196**, generated from α-diazoacetyloxiranes **195**, via intramolecular alcoholysis yielded the oxetan-3-ones **197** in 54−82% yield (Scheme 53, Table 2).[134]

The starting material **196** was obtained by reaction of α,β-epoxydiazomethyl ketones **195** with tin(IV) chloride, and the reaction occurred with retention of stereochemistry at both carbon atoms of the epoxide function.[134]

The oxetan-3-ones **197** could directly be obtained by treatment of compounds **195** with tin(IV) chloride at ambient temperatures. However, the yield of oxetan-3-ones **197** seemed to be higher when the two-step procedure was applied.

More recently, a rhodium(II) catalyzed intramolecular insertion reaction was reported to perform the cyclization toward oxetan-3-ones.[135] Oxetan-3-one-2-carboxylate **199** was prepared in this way (Scheme 54).

B.2. Oxidation Reactions

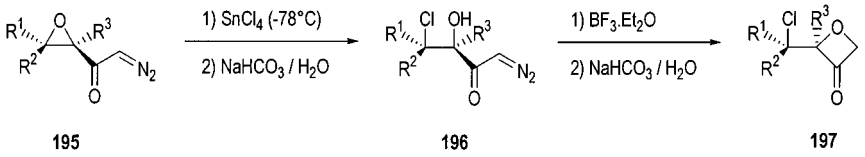
Several oxidative methods for the synthesis of oxetan-3-ones have been reported. Auto-oxidation of α,α,α′,α′-tetraphenylacetone derivatives **200** under a great variety of conditions, including heating in aqueous acetic acid in the presence of oxygen, irradiation in aqueous acetic acid, bromine in water/carbon tetrachloride, and 93% pyridine, yielded 2,2,4,4-tetraphenyloxetan-3-one **201** (Scheme 55, Table 3).[140]

In some of these cases, the reaction mechanism was assumed to proceed via a hydroperoxide intermediate.[140] 2,2,4,4-Tetraphenyloxetan-3-one **201** was also formed by dehydration of 1,3-dihydroxy-1,1,3,3-tetraphenyl-2-propanone with sulfuric acid in acetic acid.[141] The starting product was obtained after reduction of 1,3-dihydroperoxy-1,1,3,3-tetraphenyl-2-propanone, which was formed itself by electron-transfer photooxygenation of tetraphenylallene.[141]

Another method, analogous to the one applied for the synthesis of azetidin-3-ones (vide supra), involved the lead(IV) acetate oxidation of 2,2,4,4-tetrasubstituted-3-hydroxyoxetane-3-carboxylic acids **205** (Scheme 56).[143−145]

Bromination of 2,2,5,5-tetramethyltetrahydro-3-furanone **202** yielded the 4,4-dibromo derivative **203**.[142] Synthesis of 2,2,5,5-tetramethyltetrahydrofuran-3,4-dione **204** has been achieved by base treatment of **203**[142,143] or by direct oxidation of **202** with selenium dioxide in water.[144] Treatment of **204** with stronger base resulted in 2,2,4,4-tetrasubstituted-3-hydroxyoxetane-3-carboxylic acid **205** via a benzylic acid type rearrangement. For the final conversion of the 3-hydroxyoxetane-3-carboxylic acid into the oxetan-3-one **206**, several methods (among which were pyrolysis, oxidation with NBS, oxidation with dilute potassium permanganate) proved to be unsuccess-

Scheme 53

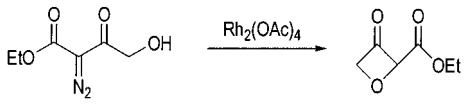


195 196 197

Table 2. Substitution Pattern and Yields for Compounds 196, 197

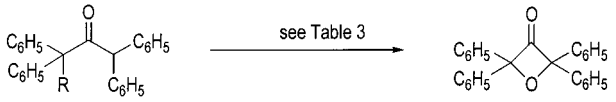
	R^1	R^2	R^3	yield **196**, %	yield **197**, %
a	C_6H_5	H	C_6H_5	81	78
b	H	C_6H_5	C_6H_5	-	54
c	*p*-$CH_3C_6H_4$	H	C_6H_5	81	82
d	C_6H_5	H	*p*-$CH_3C_6H_4$	74	70
e	C_6H_5	H	H	55	68
f	*p*-BrC_6H_4	H	H	91	76
g	α-naphth.	H	H	93	68
h	*β*-naphth.	H	H	69	79

Scheme 54



198 199

Scheme 55



200 201

Table 3. Synthesis of Oxetan-3-one 201 from Tetraphenylacetone Derivatives

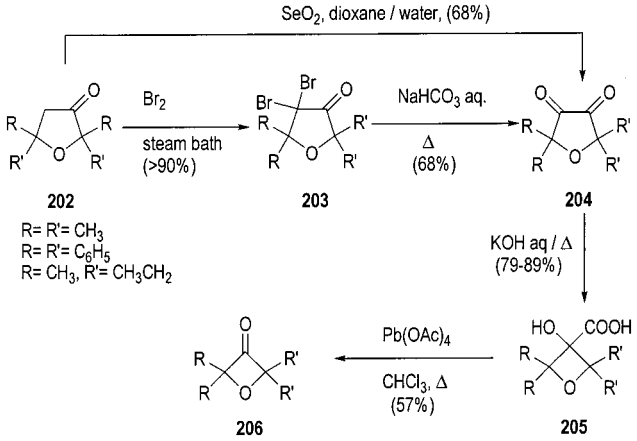
R	reagents	time, days	conditions, °C	yield **201**, %
H	O_2, 91% AcOH	2	107−110	61.5
H	N_2, 91% AcOH	2.2	107−110	
H	*hν*, 91% AcOH	105	80−100	47.3
H	Br_2, H_2O, CCl_4	43	25−50	37.5
H	93% pyridine	42	50	30
Br	93% pyridine	22	50	10
OH	Br_2, CCl_4	0.7	75−80	50

ful.[143] Only lead(IV) acetate seemed to be useful for this final transformation.[143−145] Of course, again, the scope of this reaction is limited due to the tetrasubstitution of the oxetane ring.

The most obvious way to generate the carbonyl group is of course simple oxidation of the corresponding alcohols. The oxidation of 2,2,4,4-tetraphenyloxetan-3-ol has already been described early, partially as proof for the formation of the corresponding oxetan-3-one via an alternative way.[140] This oxidation was performed with chromic anhydride in boiling acetic acid and gave the oxetan-3-one in 56% yield.

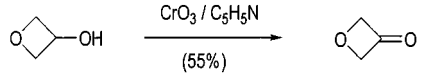
Mild oxidation of oxetan-3-ol **207** with chromic oxide and pyridine gave oxetan-3-one **208** in 55% yield (Scheme 57).[44,136] The use of permanganate, dichromate, or Oppenauer oxidation conditions were reported to fail for this substrate.[136] Alternatively, the reaction of 3-oxetanyl tosylate with dimethyl sulfoxide in the presence of tri-*n*-butylamine gave the oxetanone **208** in 33% yield.[136] Use of PCC-type oxidations has also been described.[44] As in the case

Scheme 56



202 203 204 205 206

Scheme 57

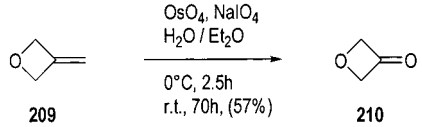


207 208

of azetidin-3-ols, oxidation of oxetan-3-ols is a delicate matter.

Oxetan-3-ones were also formed by oxidation of 3-methyleneoxetanones **209**. Treatment of oxetane **209** with osmium tetroxide and sodium periodate gave the oxetan-3-one **210** in 57% yield (Scheme 58).[108]

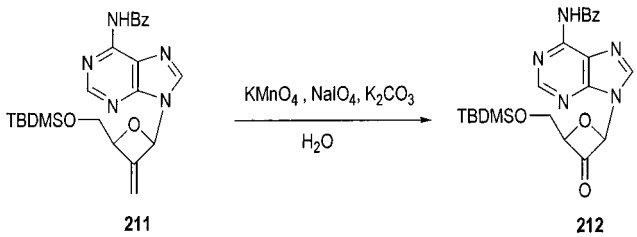
Scheme 58



209 210

The same approach has been used in the synthesis of oxetanocin derivatives, which are known antiviral nucleosides (Scheme 59).[146]

Scheme 59



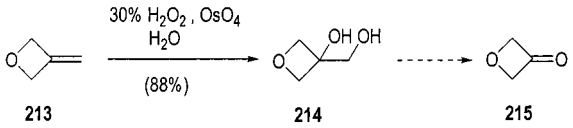
211 212

Intermediate **211** was transformed into the corresponding oxetan-3-one **212** by a Lemieux-Von Rudloff oxidation procedure.[146]

Finally, a related oxidative method to produce oxetan-3-ones also started from 3-methyleneoxetane **213** via reaction with a glycolating agent, the result-

ing glycol being cleaved to the corresponding oxetan-3-one **215** (Scheme 60).[108] In fact, this was the first

Scheme 60



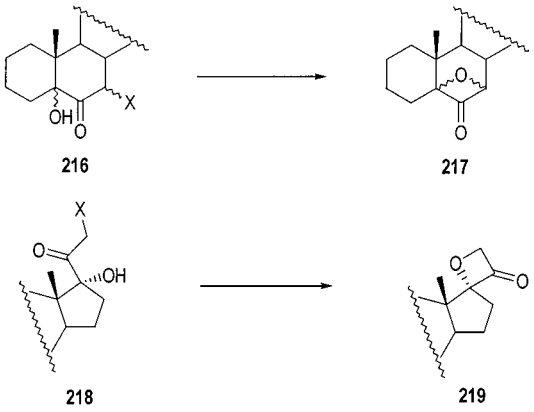
unambiguous synthesis of the parent oxetan-3-one **215**.

B.3. Intramolecular Displacement Reactions

Intramolecular displacement reactions for the preparation of oxetan-3-ones only seemed to work satisfactorily in the synthesis of steroidal oxetan-3-ones.[117] Indeed, the strategy to synthesize oxetan-3-ones by halogenation of α-ketols, followed by cyclization of the resulting acyl halides did not work.[147] Bromination resulted in the cleavage of the carbonyl−carbinol bond.

Two different steroidal oxetan-3-one structures have to be distinguished, i.e., α− or *β*-5,7-oxetan-3′-ones **217** (Scheme 61).[115,116,148,149]

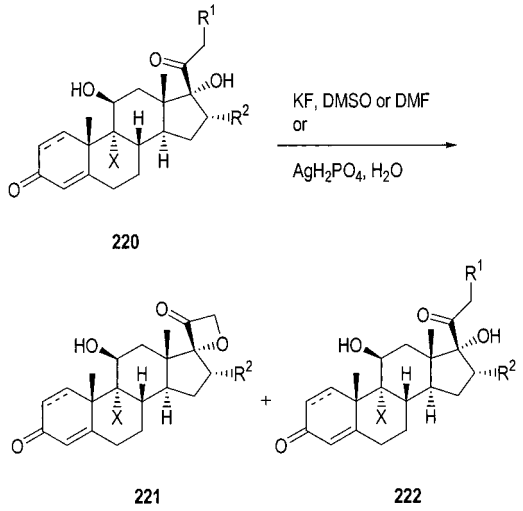
Scheme 61



On the other hand, also C17-oxetan-3′-ones **219** have been described.[114,117,118,150,151] In 1955, a pregn-4-ene-11α-ol-3,20-dione 17α,21 oxide C17-oxetan-3′-one was claimed to be obtained by acidic hydrolysis (sulfuric acid−methanol−water) of the corresponding bis-acetal-17α,21-oxide.[152] However, two following communications disapproved this finding considering the structural assignment and quoted evidence.[114,151] Apparently, under the acidic conditions, the initially formed oxetan-3-one rearranged to a five-membered ring (vide infra, C.1. Ring Opening and Ring Expansion of Oxetan-3-ones).[114,151] In both these last papers, the synthesis of steroidal oxetan-3-ones has been accomplished starting from substituted 11,17-dihydroxypregn-4-ene-3,20-dione **220** with a leaving group at C21 (Scheme 62).

Treatment of the mesylate **220** [R^1 = OMs, X = H or F, R^2 = H, (Δ^1)] with potassium fluoride in dimethylformamide or dimethyl sulfoxide furnished the substitution product **222** as the main reaction product (R^1 = F) and also the oxetan-3-one **221**.[151] This method was also expanded to some other steroidal oxetan-3-ones.[118] Treatment of the iodo-

Scheme 62

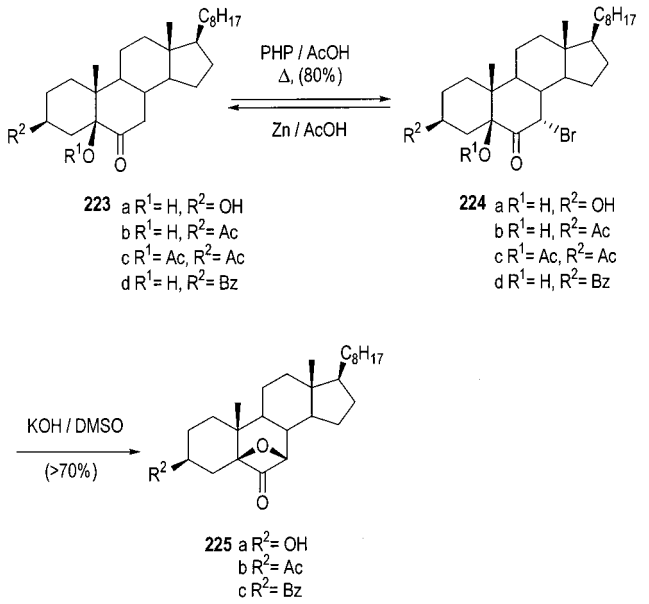


substituted **220** (R^1 = I, X = H, F, R^2 = H) with silver dihydrogen phosphate yielded, besides the steroid 24-phosphate **222** (R^1 = OP(O)$(OH)_2$) also the oxetanone **221**.[114] However, the isolation of the oxetan-3-ones **221** from both these reaction sequences occurred with low yields, and attempts to improve these yields failed.[153] Only several years later this synthesis could be optimized and the forcing reaction conditions could be smoothened. These studies showed that the α-ketomesylates **220** (R^1 = OMs, X = F, R^2 = Me, (Δ^1)) when treated with a slight excess of potassium *tert*-butoxyde in tetrahydrofuran gave the corresponding oxetan-3-one in good yields (80%).[117] The methodology also proved to work on the C21-mesylates of cortisol and deacylcortivazol (yields 76−86%).[117] Thus, reaction conditions were tempered from 16 to 24 h at 80−110 °C to a few minutes at room temperature.[117]

Ring-B cholestane oxetan-3-ones have been synthesized by intramolecular substitution reactions of 7-bromo-5-hydroxy-6-oxacholestane derivatives. In a first case, 3*β*-hydroxy-5,7*β*-epoxy-5*β*-cholestan-6-one **225** was obtained after bromination of 3*β*-substituted-5*β*-hydroxy-6-oxacholestanes with pyridinium hydrobromide perbromide (PHP) and subsequent treatment of the 7α-bromo derivatives **224** with potassium hydroxide in dimethyl sulfoxide (Scheme 63).[115] In the case of 3*β*,5*β*-acetoxy substitution (**224c**), no oxetan-3-one was obtained.[115]

It was reported that the C3-epimers of the bromoketones **224** as well as the 3-desoxy bromoketone derivative gave only poor yields of oxetan-3-ones under these conditions. A 3*β*-substituent seemed to be favorable to achieve the necessary conformational change in the A/B steroid ring system for intramolecular substitution (Scheme 63).[115] Although the poor yields of the C3-epimers and 3-desoxy derivatives, these oxetan-3-ones could be obtained by converting the 3*β*-hydroxyoxetanone **224** into its tosylate. Reflux with lithium carbonate in dimethylformamide yielded the corresponding 3α-formate ester and a 2- or 3-ene unsaturated oxetanone. The 3α-acetoxyoxetanone was obtained after saponification and acetylation, while the saturated 3-desoxyoxetanone was obtained after catalytic hydrogenation of the unsaturated oxetan-3-one.[115]

Scheme 63



The isomeric 5,7α-epoxy-5α-cholestan-6-ones have been obtained as well as starting from 7β-bromo-5α-hydroxy-6-oxocholestanes[148] as starting from 7α-bromo-5α-hydroxy-6-oxo-cholestanes.[116,149] In the former case, 7α-bromoderivatives were first epimerized by treatment with lithium bromide in dimethylformamide and converted with methanolic potassium hydroxide in dimethyl sulfoxide to give 5,7α-epoxy-5α-cholestan-6-ones.[148] In the latter case, epimerization was believed to occur under the reaction conditions, i.e., a hot lithium carbonate-dimethylformamide mixture.[116] Experiments were executed at room temperature using lithium bromide in dimethylformamide.[116] In this way, the epimerization statement was confirmed.[116]

Problems in the synthetic pathway to these 5,7α-epoxy-5α-cholestan-6-ones occurred primarily in the bromination stage (which gave several side products[148]), since the conversion of the 7β-bromo-5α-hydroxycholestan-6-ones to the corresponding oxetanones (**226** → **227**) did not require a major conformational change, as compared with the formation of the isomeric oxetanones from the 5β-hydroxycompounds (**228** → **229** or **230**) (Scheme 64).

B.4. Miscellaneous

Several oxetan-3-ones have been isolated from reaction mixtures, obtained by peracid or dimethyldioxirane oxidations of allenes.[154−161] This research was mainly done to obtain stable molecules with an allene oxide structure.[154] In these cases, the oxetan-3-one was synthesized from spirodioxides thermally,[158,160] by acid catalysis[156,158] or by preparative TLC.[159] This method, however, did not involve a straightforward and applicable synthesis of oxetan-3-ones and will not be further discussed.

1-Oxaspiro[3.5]nonan-3-one, already mentioned before,[107] could be synthesized by acidic hydrolysis of the corresponding diacetal.[162] The latter product was obtained from the photocycloaddition of cyclohexanone and ketene diacetal.[162] Other 3,3-dialkoxyoxetanes were synthesized in a similar way, but no further transformation to the oxetan-3-ones was included for these compounds.[162]

The functionalized oxetan-3-one **234** was obtained by photolysis of the chromium-(methoxy)-(methyl)-carbene complex **231** with benzaldehyde in the presence of carbon monoxide and zinc chloride as Lewis acid.[163] Remarkably, the use of all other Lewis acids led to decomposition or the formation of the β-lactone **233** (Scheme 65, Table 4).

Scheme 65

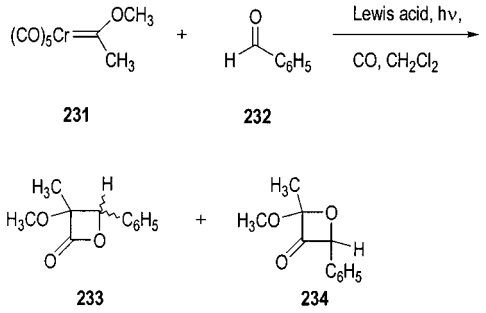


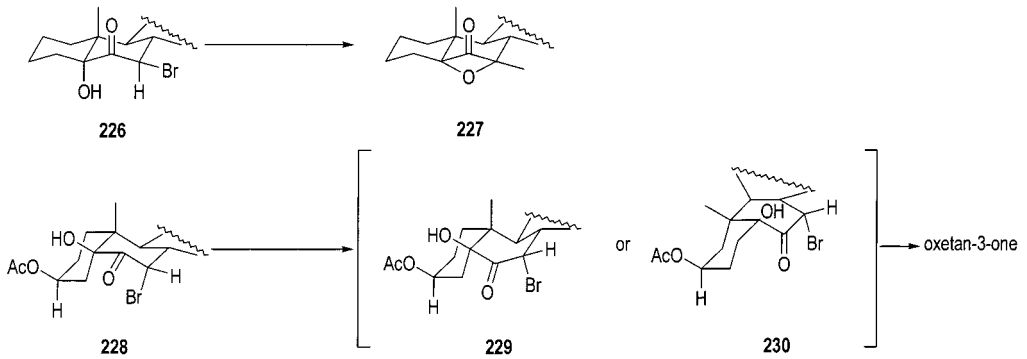
Table 4. Lewis Acids, Reaction Conditions, and Yields in the Photolysis of Chromium Carbene Complexes 231

Lewis acid	*T*, °C	product, yield
none	25	decomposition
$BF_3 \cdot Et_2O$ (0.2 equiv)	25	decomposition
MABR (0.2 equiv)[a]	25	**233**, 12%
MABR (0.2 equiv)	0	**233**, 17%
MABR (0.2 equiv)	−30	**233**, 18%
$(CH_3)_2AlCl$ (0.2 equiv)	0	**233**, 22%
$ZnCl_2$ (0.5 equiv)	25	**234**, 29%

[a] MABR = methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide).

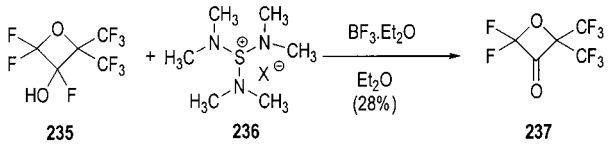
The synthesis of fluorodioxole olefin monomers by thermal decomposition of fluorinated dioxolane car-

Scheme 64



boxylic acids or the corresponding acyl chloride led to complex reaction product mixtures depending on the reaction conditions (temperature, base, solvent, counterion in the intermediate salt).[164] When the reaction was performed with sodium carbonate, oxetan-3-one **237** was isolated from the reaction mixture.[164] Alternatively, the same oxetan-3-one **237** could be synthesized by treatment of 3-hydroxy-3-fluorooxetane **235** with the tris(dimethylamino)-sulfonium salt **236** (Scheme 66).[164]

Scheme 66



2-Methyloxetan-3-one has also been isolated from the reaction mixture when 2-butanone was decomposed with oxygen at 350 °C and subatmospheric pressures.[165]

Finally, an oxetan-3-one structure has been tentatively assigned to a compound, observed by low-temperature FT-IR in the reaction mixture of the cycloaddition between an acid chloride derived ketene and an imine.[166]

C. Chemical Properties of Oxetan-3-ones

The chemical reactions that involve oxetan-3-ones as starting material consist mostly of the investigation of the lability of the oxetane ring under different conditions and of the transformation of the carbonyl group. Thus, this chapter will be divided in two parts, a first one concerning ring transformation of the oxetan-3-one structure and a second one concerning transformations of the carbonyl group.

C.1. Ring Opening and Ring Expansion of Oxetan-3-ones

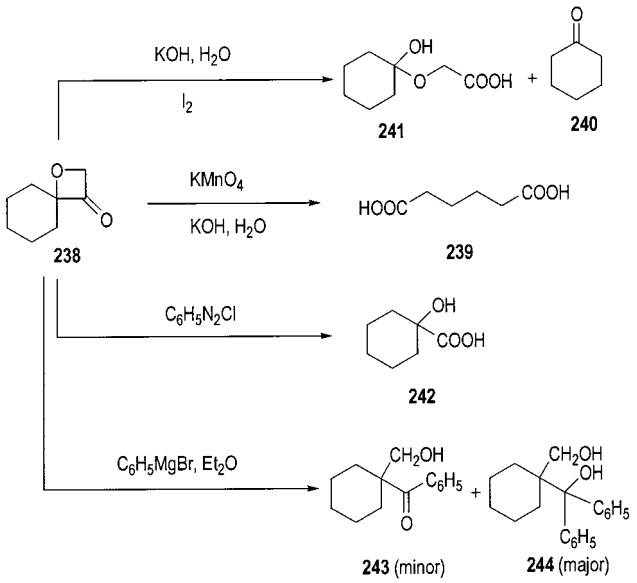
The first experiments, performed on 1-oxaspiro[3.5]-nonan-3-one **238**, exhibited the oxetan-3-one ring to be fairly stable under basic conditions, but susceptible to oxidative conditions.[107] Treatment of **238** with 2 M sodium hydroxide solution at room temperature gave the unchanged starting material (Scheme 67).[107]

Oxidation with potassium permanganate gave adipic acid **239**, and oxidation with iodine in basic medium resulted in a mixture of cyclohexanone **240** and the glycolic acid derivative **241**.[107] Treatment with phenyldiazonium chloride resulted in 1-hydroxycyclohexane carboxylic acid **242**.[107] All these reaction products were isolated in low yields.

Although Grignard reactions on oxetan-3-ones have been described to occur without problems (vide infra), the Grignard reaction of spiro-oxetan-3-one **238** led to the formation of the rearranged β-hydroxyketone **243** (minor) and the diol **244** (major) (Scheme 67).[167] After primary addition to the carbonyl group, the Grignard reagent attacked the oxymagnesium group, which led to the ring opening of the heterocyclic ring as depicted (Scheme 68).[167]

The same experiment, repeated with methyl- and benzylmagnesium halides, resulted in the diol by

Scheme 67



secondary addition of the Grignard reagent. 2-Naphthylmagnesium bromide only gave the rearranged ketone.[167]

Ring opening of tetrasubstituted oxetan-3-ones has been described to occur under several conditions (Scheme 69).

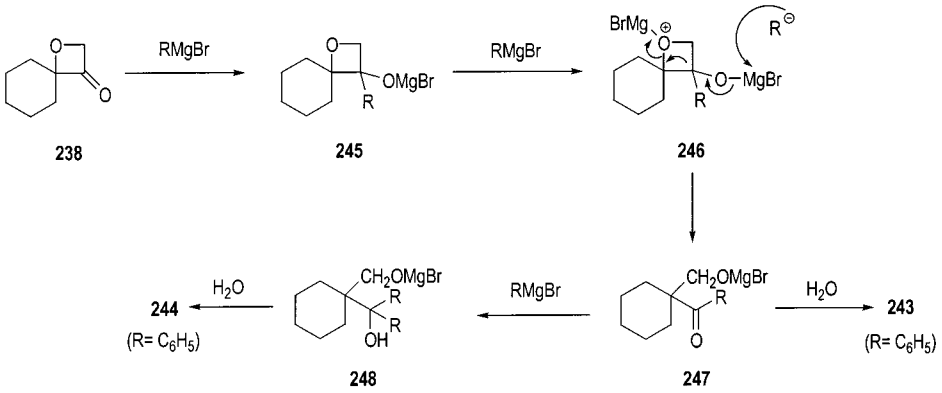
Treatment of tetraphenyloxetan-3-one **249** (R = C_6H_5) with potassium hydroxide under different conditions gave the ring opened products **250** and **254**.[140] The carboxylic acid **250** was cleaved further to α-hydroxycarboxylic acid **251** by hydrogen chloride, while hydrogen iodide in aqueous acetic acid gave a reductive cleavage to diphenylacetic acid **252** and diphenylmethane **253**. The reaction of tetramethyloxetan-3-one **249** (R = Me) with zinc in acetic anhydride resulted in the formation of α,α'-diacetoxydiisopropyl ketone **255** and α-acetoxydiisopropyl ketone **256**.[143]

Photochemical decomposition of tetrasubstituted oxetan-3-ones **257** can occur via two different pathways (Scheme 70).[168−170]

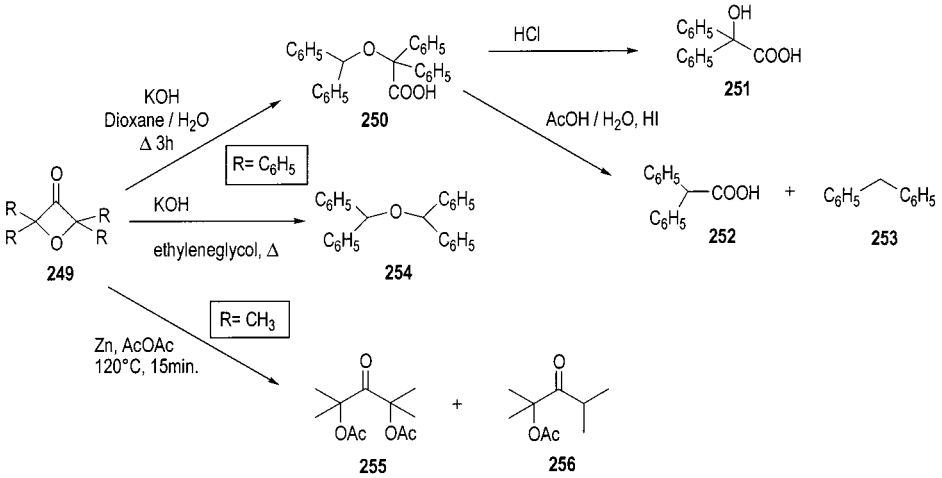
Irradiation of tetramethyloxetan-3-one **257a** (R = CH_3) with 313 nm light in solution revealed that the two pathways can be involved, depending on the solvent.[168] In polar solvents, pathway I occurred, while in nonpolar solvents, both pathways I and II were equally important. These results were later confirmed by repeating the experiments with tetraphenyloxetan-3-one **257b** (R = C_6H_5).[169−171] Tetraphenyloxetan-3-one was irradiated with 350 nm light in benzene, under conditions the oxirane **260** is known to be photostable.[170] The oxirane **260** was isolated in 36% yield.[170] Photolysis of **257b** in benzene/2-propanol solution (19:1) revealed a third pathway, i.e., reduction to 2,2,4,4-tetraphenyloxetanol.[170]

Tetraphenyloxetan-3-one **257b** has also been described as a precursor of diphenylcarbene.[171] In this paper, it was observed that diphenylcarbene, derived from different sources, exhibits different C−H insertion selectivities in low-temperature matrixes, dependent on site preferences (topochemical factors) imposed by the precursor.[171] For the parent oxetan-

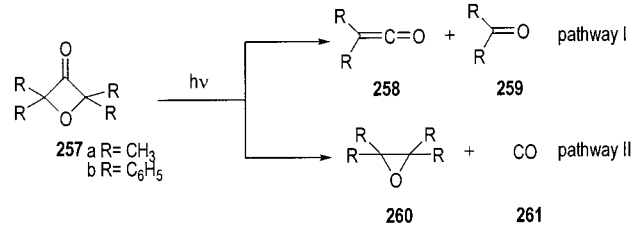
Scheme 68



Scheme 69



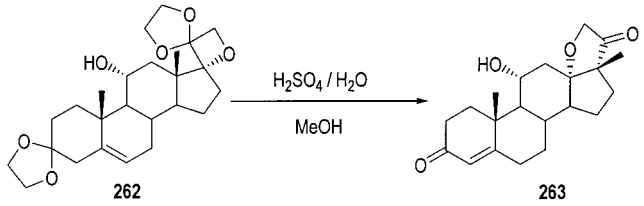
Scheme 70



3-one, unimolecular decomposition rates have been calculated.[172]

A special case of ring-opening of oxetan-3-ones with subsequent ring closure was encountered with steroidal oxetan-3-ones (Scheme 71).[114,151,152]

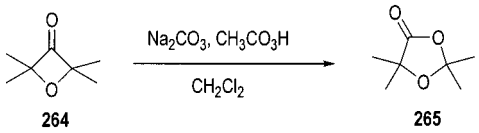
Scheme 71



Acid hydrolysis of the steroidal diacetal **262** was at first believed to give the corresponding 11α-ol-3,-20-dione-pregn-4-ene-17α,20-dioxide,[152] but two reports rejected this finding on the basis of the analysis of the spectroscopic data.[114,151] Under the reaction conditions, the intermediate oxetan-3-one was rearranged to the tetrahydrofuranone **263**.[114,151] After hydrolysis, the intermediate carbenium ion at C13 was subsequently stabilized by ring closure, rather than by double bond formation.[114]

Peracetic acid oxidation of 2,2,4,4-tetramethyloxetan-3-one **264** afforded 2,2,5,5-tetramethyl-1,3-dioxolan-4-one **265** (Scheme 72).[154] This result constitutes the only known Baeyer−Villiger type oxidation of this class of compounds.

Scheme 72

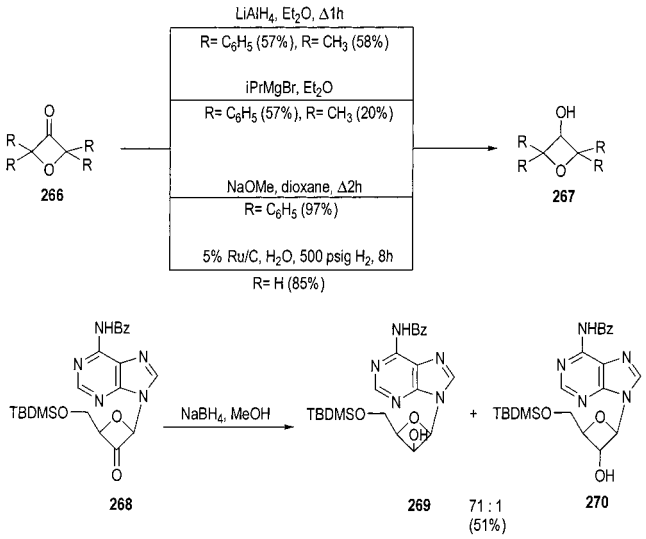


C.2. Transformations of the Carbonyl Group

The two main transformations concern the reduction of the carbonyl group and Grignard reactions on the carbonyl group. Different conditions have been applied to reduce oxetan-3-ones 2**66** to the corresponding oxetan-3-ols **267** (Scheme 73).

The reduction of tetrasubstituted oxetan-3-ones **266** has been performed with lithium aluminum hydride and isopropylmagnesium bromide.[140,144] In the case of tetraphenyloxetan-3-one **266** (R = C_6H_5), the reduction to **267** (R = C_6H_5) was also achieved with sodium methoxide in dioxane in good yields.[140] The reduction has also been described by catalytic

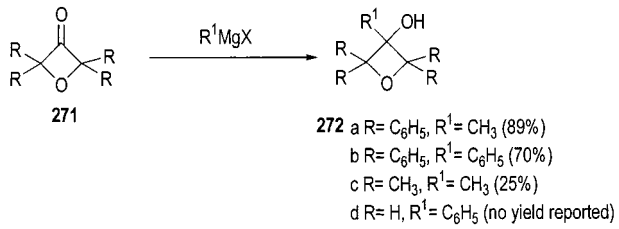
Scheme 73



hydrogenation.[136,173] A more complex oxetan-3-one **268** was also converted to the corresponding oxetan-3-ols **269** and **270** with sodium borohydride in methanol.[146]

The described Grignard reactions of oxetan-3-ones are summarized in Scheme 74.

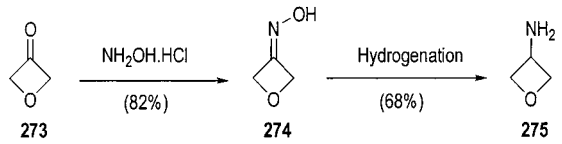
Scheme 74



Tetraphenyloxetan-3-one **271** (R = C_6H_5) was reacted with both methyl- and benzylmagnesium halide to give the tertiary alcohols **272a**,**b** in good yields.[140] In these cases, the reaction was performed in toluene or dibutyl ether because of the low solubility of oxetan-3-one **271** (R = C_6H_5) in diethyl ether. Grignard reaction of **271** (R = Me) with methylmagnesium iodide gave the oxetan-3-ol **272c** in rather poor yield.[144] The reaction of phenylmagnesium bromide with oxetan-3-one **271** (R = H) furnished the corresponding oxetan-3-ol **272d**.[174] As can be seen from these results, Grignard reactions on oxetan-3-ones have been mainly performed on tetrasubstituted oxetan-3-ones. The yields seem to increase with increasing steric hindrance of the C-2 and C-4 substituents.

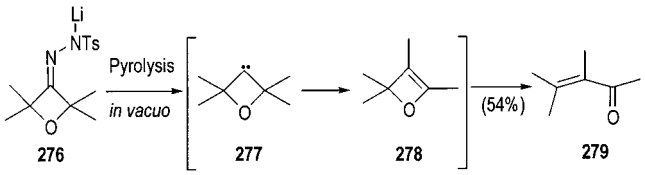
Oxetan-3-one **273** reacted with hydroxylamine hydrochloride to give the oxime **274** (Scheme 75).

Scheme 75



Subsequent hydrogenation of the oxime **274** gave the 3-aminooxetane **275**.[173] Also the *N*-tosylhydrazone has been prepared. The lithium salt **276** of this hydrazone has been pyrolyzed in vacuo to yield 3,4-dimethyl-3-penten-2-one **279**.[175] The proposed mechanism for this reaction is shown in Scheme 76,

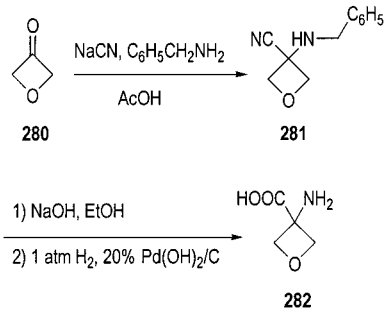
Scheme 76



entailing the generation of a carbene **277** and a subsequent migration of a methyl group. These experiments were conducted in analogy to the ones to synthesize alkylidene-substituted thiiranes from hydrazone-derivatives of thietanones (vide infra).

A suitably substituted oxetan-3-one has been transformed into the biologically interesting new amino acid **282**, containing the oxetane substructure, by a reaction sequence completely analogous to the one already described for the corresponding azetidin-3-one, aminocyanation of the carbonyl group, subsequent alkaline hydrolysis and hydrogenolysis (Scheme 77).[44]

Scheme 77



Finally, 2,2,4,4-tetramethyl- and 2,2,4,4-tetraphenyloxetane have been prepared by Wolff−Kishner reduction of the corresponding oxetan-3-ones.[176]

As can be seen from the overview of these reactions of oxetan-3-ones, the reactivity is less explored than in the case of azetidin-3-ones (vide supra). Both classes of compounds have a peculiar and rich synthetic potential, which is definitely underdeveloped at present. Suprisingly, some potential reactivities of the oxetan-3-one ring system remain unexplored, e.g., aldol reactions and imine formation have not yet been performed.

IV. The Chemistry of Thietan-3-ones

The chemistry of oxetan-3-ones is less developed than the chemistry of azetidin-3-ones, but the chemistry of thietan-3-ones **283** is even less common (Figure 6). However, in contrast to azetidin-3-ones

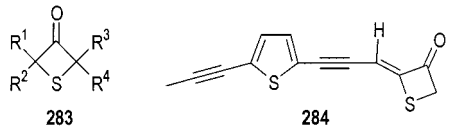


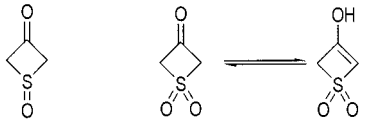
Figure 6.

and oxetan-3-ones, the thietan-3-one skeleton has already been isolated from natural sources.

From the plant *Berkheya barbata* (L.f.) Hutch., (2*Z*)-2-{3-[5-(1-propynyl)-2-thienyl]-2-propynylidene}-3-thietanone **284** was isolated.[177] At first, the compound was believed to possess another structure due to the paucity of natural products that contain the unusual thietanone ring system. Synthesis, however, showed that the proposed structure **284** matched the spectroscopic data retrieved from the natural product (vide infra).

The far-infrared and microwave spectrum of thietan-3-one have been studied to obtain information about the ring-puckering and vibration of this small ring heterocycle.[178,179]

This chapter will also cover partially the chemistry of the related 3-thietanone-1-oxide **285** and 3-thietanone-1,1-dioxide **286** (Figure 7).



285 **286** **287**

Figure 7.

Where appropiate, syntheses or reactivities of compounds **285** and **286** will be mentioned. Thietan-3-one-1,1-dioxide **286** can also occur in its enolic form **287**. However, NMR and IR data obtained from this compound in deuterium oxide, tetrachloroethane, or dimethyl sulfoxide showed no evidence for this tautomerism.[180,181] The occurrence of the enolic form in substituted thietan-3-ones-1,1-dioxides has been reported.[182,183]

This chapter will consist of two parts that will deal with the synthesis of this small sulfur-containing heterocycle and with further chemical transformations, respectively.

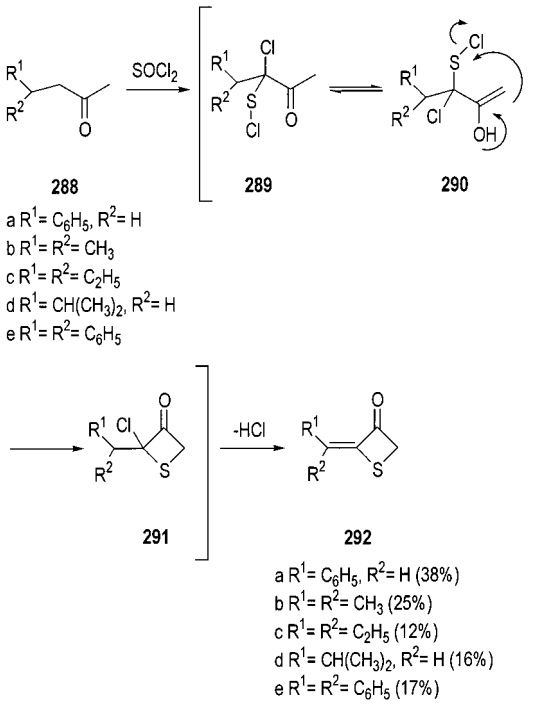
A. Synthetic Methods for Thietan-3-ones

A.1. Synthesis from Acyclic Precursors

The synthesis of thietan-3-ones was achieved starting from simple ketones. 4-Phenyl-2-butanone **288a** was treated at room temperature with an excess thionyl chloride and catalytic amounts of pyridine (Scheme 78). 2-Benzylidenethietan-3-one **292a** was isolated.[184,185] Other alkylidene thietanones have also been synthesized in this way. The reaction is believed to proceed via the formation of sulfenyl chloride **289** by a Hell-Volhard-Zelinsky addition of thionyl chloride to the enol form of the ketone **288** and consequently conversion to a sulfenyl chloride by a Pummerer type rearrangement.[184,185]

These experiments were repeated later, and **289b** and **291b** could be isolated in 58 and 5% yield, respectively.[186,187] More recently, tetrasubstituted thietan-3-ones were synthesized from 1,1,3,3-tetrasubstituted propan-2-one derivatives when treated with sulfur dichloride to give the intermediate sulfenyl chlorides. The latter compounds were converted to the thietan-3-ones by reaction with potassium *tert*-butoxide in tetrahydrofuran.[188] Earlier, several amides

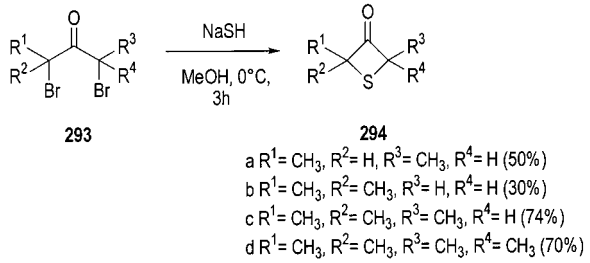
Scheme 78



derived from acetone dicarboxylic acid derivatives were reported to react with thionyl chloride, giving 3-oxo-2,4-thietanedicarboxamide-1-oxide derivatives.[189] This was the first synthesis of a thietan-3-one-1-oxide.

Several reports included the synthesis of thietan-3-ones starting from α,α′-dibromoketones (Scheme 79).[190−197]

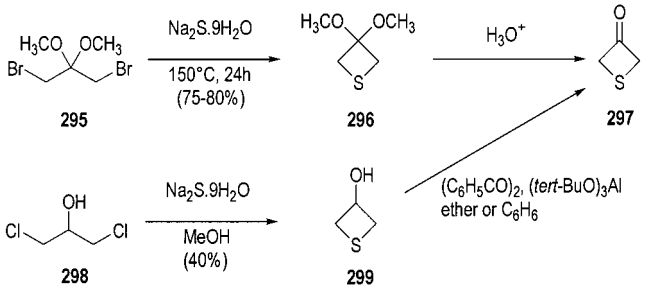
Scheme 79



The best results were obtained by the use of sodium hydrogen sulfide, generated from sodium in methanol, saturated with hydrogen sulfide.[191−193] Earlier conditions using sodium disulfide proved less reactive, but also in this case the formation of the thietan-3-one was observed.[190] The reaction of α,α′-dibromoketones **293** not only afforded thietan-3-ones **294**, but also α,α′-dimercapto ketones were formed as side products, which upon dehydration at sulfur gave 1,2-dithiolan-4-ones.[193] Unsubstituted thietan-3-one and 2-methylthietan-3-one could not be synthesized in this way, indicating the importance of the *gem*-effect for ring closure.[193] However, cyclization of 3,5-dichloro-4-oxopentanoic acid under the same conditions did result in the isolation of thietan-3-one-2-carboxylic acid.[192]

Basically the same reaction was performed with sodium sulfide on 1,3-dibromoacetone dimethyl acetal **295**[198] and 1,3-dichloropropan-2-ol **298** (Scheme 80).[199]

Scheme 80



Treatment with sodium sulfide gave thietan-3-one dimethyl acetal **296** and 3-thietanol **299** in 80 and 40% yield, respectively. The former compound was hydrolyzed with mineral acids to afford the thietan-3-one **297**,[198] while the latter compound was oxidized to the thietan-3-one **297** with benzil and tri-*tert*-butoxyaluminum.[199] Further oxidation of this thietan-3-one with perphthalic acid or peracetic acid in benzene gave the corresponding thietan-3-one-1,1-dioxide in good yields (83−97%).[200] The use of a hydrogen peroxide-acetic acid system resulted in complex reaction mixtures of unreacted starting material, thietan-3-one-1,1-dioxide, thietan-3-one-1-oxide, and rearrangement products.[200]

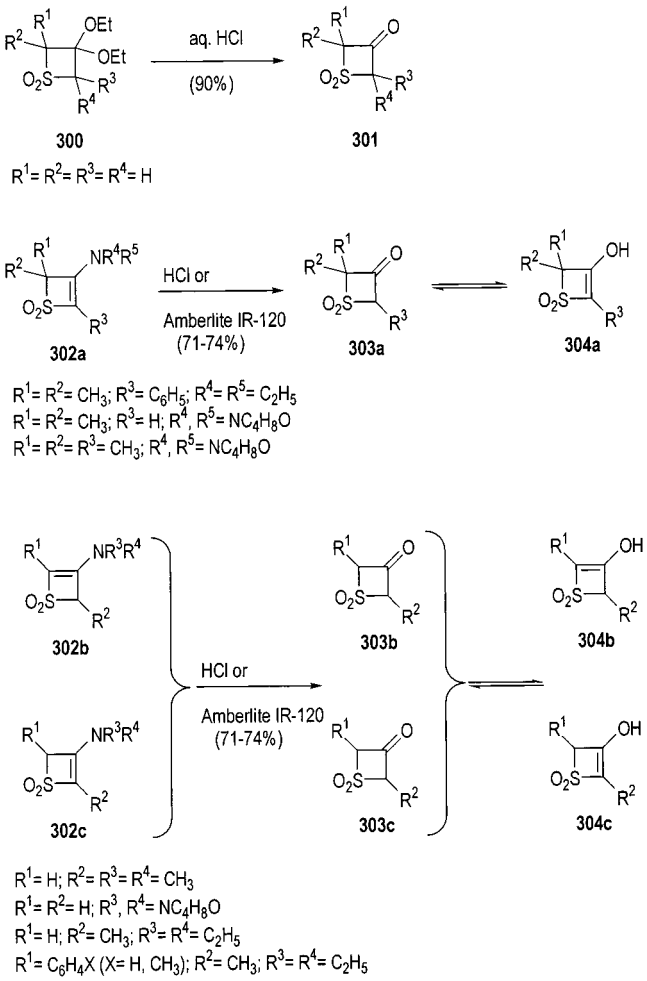
Analogous to the synthesis of thietan-3-one **297** from the acetal **296** by acidic hydrolysis, thietan-3-one-1,1-dioxides also were synthesized in this way (Scheme 81).[183,201−205]

The acetal **300** was obtained from the reaction of 1,1-diethoxyethylene and methanesulfonyl chloride in the presence of triethylamine (yield 79%).[201−203] Subsequent hydrolysis with hydrochloric acid gave the corresponding thietan-3-one-1,1-dioxide **301** ($R^1 = R^2 = R^3 = R^4 = H$) in 90% yield.[201−203] The reaction has also been performed with halo-substituted methanesulfonyl chlorides.[183] In this case, hydrolysis did not result in the corresponding thietan-3-one-1,1-dioxides **301** ($R^1 = R^2 = R^3 = H$, R^4 = Cl, Br, or I) but in halomethyl 2-methyl-2-propenyl sulfone derivatives.[183] Reaction of phenylmethanesulfonyl chloride with [(1-ethoxy-2-methyl-1-propenyl)oxy]trimethylsilane and subsequent hydrolysis gave the thietan-3-one-1,1-dioxide **301** (R^1, $R^2 = CH_3$; $R^3 = H$, $R^4 = C_6H_5$).[204] The hydrolysis of 3-(dialkylamino)thiete-1,1-dioxides **302** also resulted in the formation of the corresponding thietan-3-one-1,1-dioxides **303**.[180−182,205−209] The 3-dialkylaminothiete-1,1-dioxides **302** were obtained from the cycloaddition of alkylsulfonyl chlorides and ketene O,N-acetals or aminals[180−183,209] or from the cycloaddition of alkylsulfonyl chlorides and alkynylamines.[206] Many different compounds **302** have been synthesized in this way. The hydrolysis was performed with an acidic exchange resin (Amberlite IR-120)[180,181,206] or concentrated hydrochloric acid in water.[207,209]

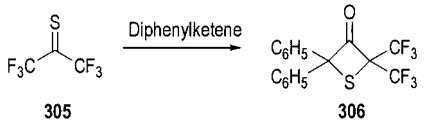
Thietan-3-ones were also obtained by the cycloaddition reaction between 1,1,1,3,3,3-hexafluoro-2-propanethione **305** and diphenylketene, which gave compound **306** via a [2+2] cycloaddition reaction (Scheme 82).[210]

The cycloaddition of thiobenzophenone and diphenylketene has been reported to give 2,2,4,4-

Scheme 81



Scheme 82

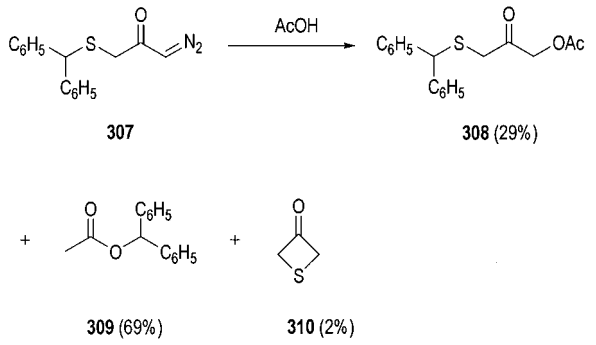


tetraphenylthietan-3-one in 85% yield.[211] However, the compound thereby obtained exhibited an IR absorption at 1720 cm^{-1}, i.e., in the region of the isomeric thiolactones.[212] Thietan-3-ones exhibit an IR absorption near 1770 cm^{-1}, indicating there is no transannular interaction because of the strain in the heterocycle.[213] Thus, the previous experiment was repeated, and results indicated the synthesis of thiolactones instead of the first reported thietan-3-ones.[212] From this and the foregoing result, it might be concluded that for the [2+2] cycloaddition with diphenylketene, thioketones need to be strongly activated.

Thietan-3-one **310** was also synthesized, albeit in low yield, by acetolysis of the α-diazoketone **307** (Scheme 83).[137,214,215]

On treatment of phenylthiodiazoketones with perchloric acid the stable cyclic β-oxosulfonium perchlorates are formed by an intramolecular cyclization.[216] The thietan-3-one derivatives exhibit an IR absorption at 1812 cm^{-1} and are reported to be stable for a few weeks.[216] Further reaction of these compounds with, for instance, thioanisole or triphenylphosphine,

Scheme 83



gave the corresponding acyclic salts, i.e., methyl-(phenyl)[(phenylsulfanyl)carbonyl]sulfonium and [2-oxo-2-(phenylsulfanyl)ethyl](triphenyl)phosphonium perchlorates, respectively.[216] Stable cyclic sulfonium ylides, including ylides with a thietan-3-one structure, have been prepared by rhodium(II)-catalyzed decomposition of ethyl 2-diazo-3-keto-4-thioethylbutanoate.[217]

Treatment of α-diazo-1,2-diphenylethanone with sulfur dioxide was reported to give a mixture of 2-benzoyl-2,4,4-triphenyl-3-thietanone-1,1-dioxide and the corresponding 2-thietanone-1,1-dioxide.[218] This interpretation of the spectroscopic data of the reaction products turned out to be erroneous, and two other structures were proposed.[219]

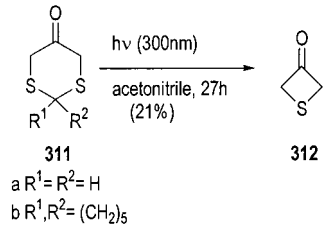
The synthesis of 2-phenylthietan-3-one-1,1-dioxide has also been reported starting from ethyl (benzylsulfonyl)acetate upon treatment with sodium hydroxide.[220] The main product was the corresponding carboxylic acid (65%), while the thietan-3-one-1,1-dioxide was isolated in a yield of 15%.[220]

Finally, a steroidal thietan-3-one has been isolated in very low yield from the reaction of a homo-3D derivative of 17-acetoxy-(21-acetylthio)-4-pregnene-3,20-dione with excess sodium azide in methanol.[221]

A.2. Synthesis by Ring Transformations

Thietan-3-ones have been synthesized by a variety of procedures involving ring contraction or ring expansion of other sulfur-containing heterocycles. For instance, irradiation of 1,3-dithiane-5-one in acetonitrile with 300 nm light for 27 h gave the thietan-3-one **312** in 21% yield (Scheme 84).[222] Similarly, also

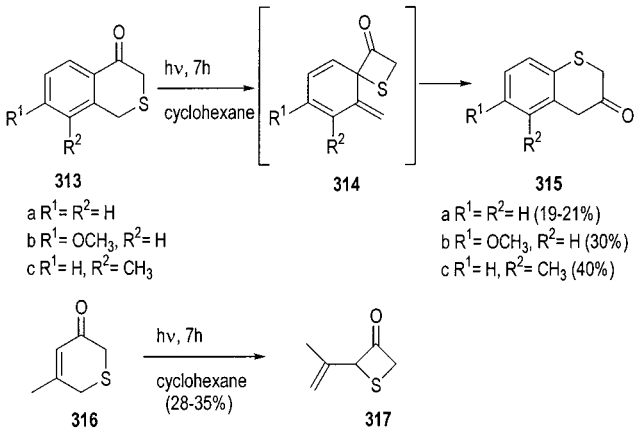
Scheme 84



311b gave the thietan-3-one **312** after irradiation in Freon-113.[222]

Thietan-3-ones were believed to be intermediate structures in the photochemically induced reactions of isothiochroman-4-ones **313** (Scheme 85).[223,224] Irradiation of compounds **313** led to the isolation of thiochroman-3-one **315** in low yields. The reaction

Scheme 85

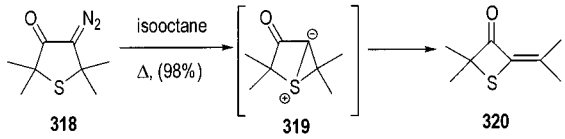


was believed to proceed via the thietan-3-one triene intermediate **314**. After irradiation for a short time, reaction mixtures exhibited an IR absorption at 1770 cm^{-1} what might be an indication for the formation of the initial photoproduct **314**.

Further photochemical rearrangement of the intermediate **314** was probably the result of excitation of the triene moiety, which was checked with the photolysis of 5-methyl-2,3-dihydro-2H,6H-thiopyran-3-one **316** since no further photochemical rearrangement could take place in this compound if the triene system was responsible for further reaction. Indeed, thietan-3-one **317** proved to be stable under the reaction conditions and was obtained with a yield of 28−35%.[223,224]

Another synthesis of thietan-3-ones involving ring contraction started from the cyclic α-diazoketone **318** (Scheme 86).[225−227]

Scheme 86

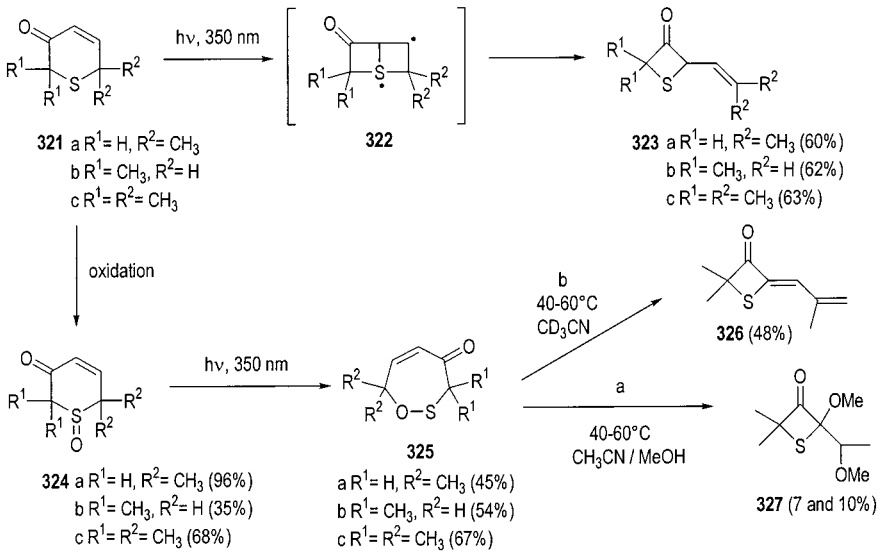


The α-diazoketone was prepared starting from 2,5-dibromo-2,5-dimethyl-3,4-hexanedione, which was reacted with sodium sulfide.[225] The resulting 2,2,5,5-tetramethyl-3,4(2*H*,5*H*)-thiophenedione was converted to the α-diazoketone **318** via the tosylhydrazine. Thermally induced decomposition gave the thietan-3-one **320** in quantitative yield.[225] The proposed structure **320** was firmly established by crystallographic analysis of the cycloaddition product of **320** with tetrachloro-*o*-quinone.[226]

Photoisomerization of thiir-3-ones **321** when irradiated in acetonitrile, benzene or 2-propanol gave selectively the thietan-3-ones **323** (Scheme 87).[228,229]

The sulfuranyl-alkyl singlet biradical **322** was proposed as intermediate in this reaction on the basis of the observation that the efficiency of the rearrangement was not dependent on or sensitive to the stability of the displaced radical group and that the reaction was not quenched by naphthalene.[228] Oxidation of thiir-3-ones **321** with 3-chloroperbenzoic acid yielded the sulfoxides **324** that rearranged to the seven-membered cyclic sulfenates **325** when irradi-

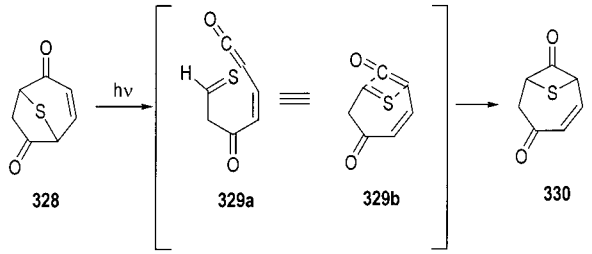
Scheme 87



ated.[229] Heating of these sulfenates in deuterated acetonitrile gave the thietan-3-one **326**, while performing the irradiation of **325** in methanol afforded two diastereoisomeric products **327** in 7 and 10% yield, respectively.[229]

Thietan-3-ones are also reported being part of a molecule as substructure (Scheme 88).

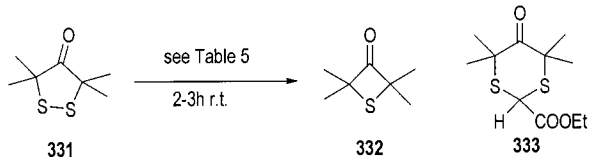
Scheme 88



The photolysis of the δ-thia-α,β-unsaturated ketone **328** resulted in the formation of thietan-3-one **330**.[230,231] The overall reaction consisted of a 1,3-migration of the sulfur atom. Further evidence was supplied that the reaction took place via a [2+2]-cycloaddition of the vinylketene intermediate **329**.[230]

Reaction of cyclic disulfides with carbenes, generated from catalytic or photochemical decomposition of diazo compounds, resulted in the formation of tetrasubstituted thietan-3-ones (Scheme 89, Table 5).[232]

Scheme 89



The products **332** resulted from S−S insertion of the disulfide and subsequent desulfurization. Only in the case of ethyl diazoacetate (entry d, Table 5), the reaction only gave the insertion product **333**.[232]

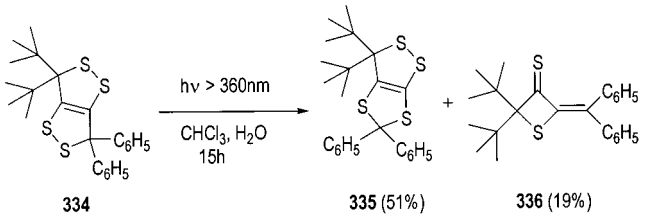
Tetramethyl-3-thietanone was reported to form stable complexes with diiron nonacarbonyl.[233] Thietan-3-ones were also obtained by decomposition of another diiron nonacarbonyl complex. The complex formed by 2-*tert*-butyl-3-(diphenylmethylene)thiirane and diiron nonacarbonyl decomposed when heated in toluene in a sealed tube to give rise to the corresponding alkylidenethietan-3-one with a yield of 45%.[234] When substituted 2-(1,2-propadienylidene)-thiiranes and 2-ethenylidene-3-methylenethiiranes were decomposed thermally or photochemically, substituted 2-ethenylidene-3-thietan-3-thiones were isolated from the reaction mixture, together with other rearranged products.[235]

Table 5. Reaction Partners and Yields in the Synthesis of 332

	diazo compound	catalyst	**332**, yield, %
a	$N_2C(C_6H_5)_2$	CuCl	28
b	$N_2C(C_6H_5)_2$	$[Rh(OAc)_2]_2$	29
c	$N_2C(COOCH_3)_2$	[*hν*]	33
d	$N_2CHCOOC_2H_5$	CuCl	

Rearrangement of the 1,2-dithiole **334** furnished mainly the 1,3-dithiole **335** and thietan-3-thione **336** (Scheme 90).[236]

Scheme 90



B. Chemical Properties of Thietan-3-ones

The main reactivity of thietan-3-ones is very similar to the reactivity of azetidin-3-ones and oxetan-3-ones. Principle transformations include of course transformations of the carbonyl group and aldol reactions. Further, also ring transformations, including ring expansion and ring opening, have been described.

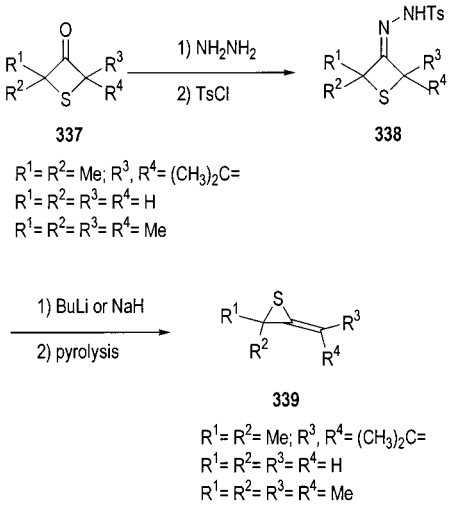
B.1. Transformations of the Carbonyl Group

Of course, this transformation includes the reduction of the carbonyl group to obtain the corresponding thietan-3-ol. Reduction was performed with sodium borohydride in methanol/water[198] or in methanol.[191] The thietan-3-one-1,1-dioxide was also reduced to the corresponding thietan-3-ol-1,1-dioxide under the action of diborane in dioxane.[201,202]

Thietan-3-amines have been synthesized by reduction of thietan-3-one oximes, obtained from the reaction of thietan-3-ones and *O*-substituted hydroxylamines.[237] 3-Amino-2,2,4,4-tetramethylthietane has also been obtained via the Leuckart reaction between 2,2,4,4-tetramethyl-thietan-3-one and dimethylformamide, using boric acid or aluminum salts as catalysts.[238] Thietan-3-one-1,1-dioxides have been reacted with monosubstituted ureas to give thietylureas, which are reported to have antihypertensive activities.[239] Also, a Grignard reaction of phenylmagnesium bromide on thietan-3-one itself has been reported.[240]

The thietan-3-ones **337** have also been converted in the corresponding thietan-3-one hydrazones **338** (Scheme 91).[175,195,196,227,241]

Scheme 91



This research was mainly done toward the synthesis of alkylidene thiiranes **339** and to explore the further reactivity of the latter compounds. The thietan-3-one hydrazones **338** were pyrolyzed at 130−160 °C and pressures of 10^{-4}−10^{-3} Torr, after their conversion into the corresponding salt by treatment with butyllithium[195,227,241] or sodium hydride.[175,196] Direct preparation of hydrazone **338** from thietan-3-one **337** and tosylhydrazine only gave **338** in poor yields (38% or lower).[195,196,241] These low yields were circumvented by reacting thietan-3-one **337** first with unsubstituted hydrazine, which gave the corresponding thietan-3-one hydrazone in good yield (97%).[196] Reaction of the hydrazine with tosyl chloride in the presence of a base finally afforded the hydrazone **338**.[196]

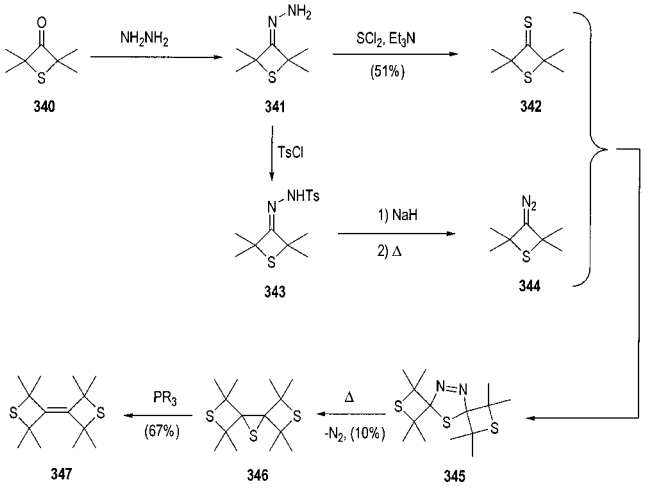
The reaction of 2,2,4,4-tetramethylthietan-3-one-1,1-dioxide with hydrazine was not so unambiguous. Attempts to react tetramethylthietan-3-one-1,1-dioxide with hydrazine in ethanol led to the isolation of the ring-opened substituted sulfonylpropanohydrazide.[242] The conversion to the thietan-3-one-1,1-dioxide hydrazone was only obtained when doing the reaction in a diluted dioxane solution. Performing the reaction in a more concentrated solution resulted in a mixture of the desired hydrazone and the corresponding diazine.[242]

Other reactions of thietan-3-one-1,1-dioxide included thioacetal formation, yielding a 1,3-dithiane structure.[183] Reaction of thietan-3-one-1,1-dioxide with aromatic amines gave the corresponding imines in rather poor yields (12−48%). These latter compounds also exhibited keto−enol tautomerism.[183] In general, the reaction of thietan-3-one-1,1-dioxides with nucleophiles is not so unambiguous since the sulfoxide group might stabilize the negative charge on the methylene group after ring opening.

Several reports included the transformation of thietan-3-ones or thietan-3-one-1,1-dioxides in the corresponding thioketones. In the case of thietan-3-one, this conversion has been accomplished by the use of a mixture of trimethyl orthoformate, hydrogen sulfide, and hydrochloric acid[243] or the use of dichlorodisulfane on the corresponding hydrazone.[244] For thietan-3-one-1,1-dioxides, this conversion has been performed by the use of phosphorus pentasulfide in pyridine.[200] In the latter case, this transformation was done to avoid Wittig reactions of thietan-3-one-1,1-dioxides. It has been reported that Wittig reactions on either thietan-3-ones or thietan-3-one-1,1-dioxides caused problems.[200] To avoid these problems, thietan-3-one-1,1-dioxides were converted into the corresponding thioketones, that were reacted with diazoalkanes. The intermediate thiiranes underwent desulfurization to the corresponding alkenes when treated with triphenylphosphine.[200]

Thietan-3-ones **340** were converted, using known transformations, into the corresponding thioketone **342** and the diazo compound **344** (Scheme 92).[244]

Scheme 92



These compounds reacted with each other to give thiadiazoline **345**. By heating the thiadiazoline until nitrogen loss had stopped, the thiirane **346** was obtained. Final desulfurization proceeded smoothly with tri-*n*-butylphosphine, trimethyl phosphite, or tri(diethylamino)phosphine.[244] In this way, the alkene **347** was obtained. An almost completely analo-

gous pathway has been described for thietan-3-one-1,1-dioxides.[242] Reaction of the thioketone and the diazo compound derived from thietan-3-one-1,1-dioxide gave the corresponding dihydrothiadiazole in modest yield (21%) because of the instability of the diazocompound. Further transformation to the alkene proceeded without further difficulties.[242] Further pyrolysis of the alkene gave (2,2,3,3-tetramethylcyclopropylidene)thietane-1,1-dioxide derivative **348** and 4-isopropyl-2,5-dimethyl-3-(1-methylethylidene)-1,4-hexadiene **349** (Figure 8).[242]

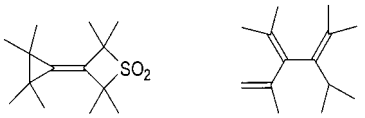
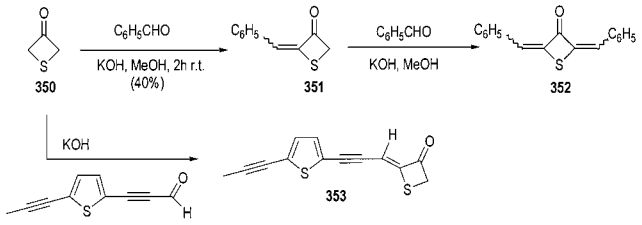


Figure 8.

B.2. Aldol Reactions

The aldol reaction of 2-benzylidene-3-thietanone **351** with benzaldehyde in the presence of sodium hydroxide was described to give the bisbenzylidene-3-thietanone **352** (Scheme 93).[184]

Scheme 93



Preliminary attempts to perform an aldol reaction between thietan-3-one **350** and benzaldehyde gave immediately the bisbenzylidene derivative **352**.[177] Compounds, possessing the general structure **352**, were used in photoresists as UV-absorbing agents to suppress halation and notching in pattern formation on highly reflective substrates.[245] Using more controlled reaction conditions also permitted isolation of the monosubstituted thietan-3-one **351**.[177] Reaction of the latter compound with thionyl chloride resulted in chlorination of the double bond.[187] The aldol reaction of thietan-3-one **350** with para-substituted benzaldehydes gave rise to reaction mixtures of the bisbenzylidene derivatives, the benzylidene derivatives, and nondehydrated products.[246] Reaction with formaldehyde gave the tetrakis(hydroxymethyl)-thietan-3-one.[246] The aldol reaction performed on thietan-3-one **350** was also the key step in the synthesis of the natural product **353**.[177]

B.3. Ring Transformations

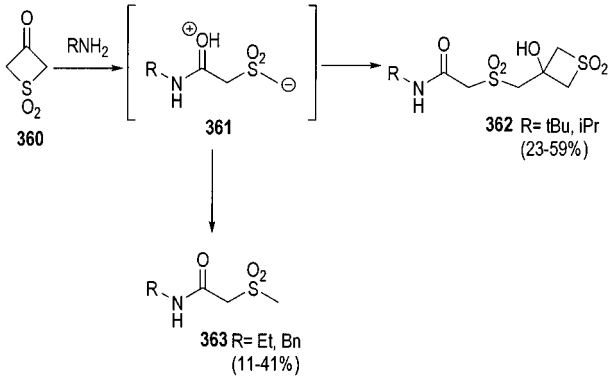
Thermolysis of thietan-3-ones at 900 °C in vacuo yielded ketene and thioxomethane.[247] To obtain sulfenes, thermolysis of substituted thietan-3-one-1,1-dioxides at 930−950 °C was performed.[248,249] In this case, only the formation of the corresponding alkenes (yield 96−98%) could be observed. However, photochemical decomposition of thietan-3-one-1,1-dioxide in acetonitrile or acetonitrile-methanol mixture resulted in the formation of ketene and sulfene.[250] These authors also stated that thietan-3-one-1,1-dioxide in a 90% acetonitrile−10% methanol mixture was present as thietan-3-one-1,1-dioxide and as the corresponding hemiacetal (ratio 1 to 9).

Photochemically induced decomposition of isopropylidenethietan-3-one **354** gave the products **357** and **359** by a radical ring opening, followed by two different pathways for the rearrangement (Scheme 94).[226]

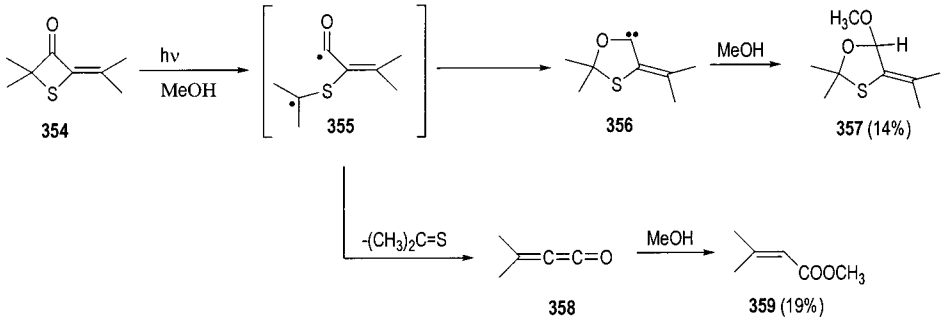
Also reductive desulfurization of thietan-3-ones was reported to give the corresponding substituted ketones.[210]

Ring opening of thietan-3-ones and thietan-3-one-1,1-dioxides has been reported to occur under the action of primary and secondary amines. Reaction of thietan-3-one with secondary amines such as morpholine did not give enamines but the ring opened 2-oxopropionthioamides.[251] The same reaction performed on 2-methylthietan-3-one-1,1-dioxides gave ring opening to the *N*,*N*-dialkyl-2-(methylsulfonyl)-acetamides.[206] The reaction of thietan-3-one-1,1-dioxide **360** with primary amines afforded the products **362** or **363** via the intermediate **361**.[183] The

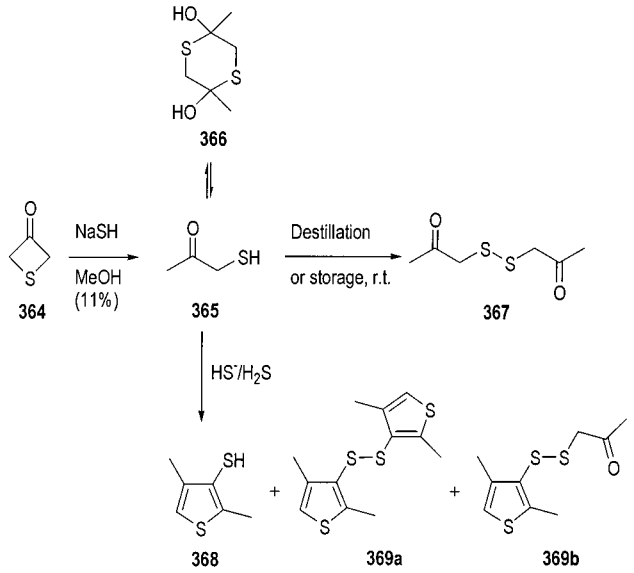
Scheme 95



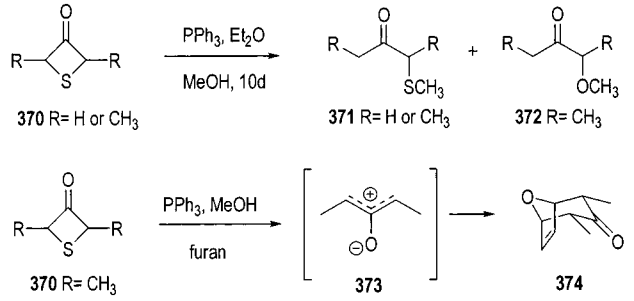
Scheme 94



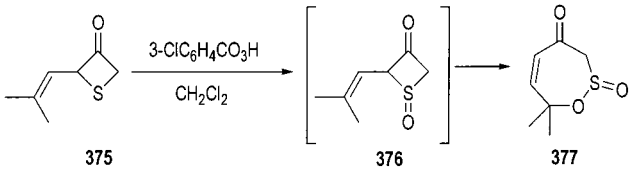
Scheme 96



Scheme 97



Scheme 98



pathway that was followed depended on the amine used (Scheme 95).

Thietan-3-one **364**, in reaction with sodium hydrogen sulfide, afforded 1-mercapto-2-propanon **365**, which was in equilibrium with its dimer (Scheme 96).[193,252] The dimer **366** degradated on heating to the monomer **365**. Storage at room temperature and air resulted in oxidation to the product **367**.[193]

Further reaction of **365** by an aldol reaction furnished the thiophene **368** and the dimers **369**.[193]

Another type of ring opening of thietan-3-ones was achieved by reaction with triphenylphosphine, tri-*n*-butylphosphine, or tris-(4-methoxyphenyl)phosphine in methanol (Scheme 97).[253]

However, when the reaction was performed in a methanol−furan (1:1) mixture, 2-endo,4-endo-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **374** was obtained, probably from the [4+3] cycloaddition of furan with 1,3-dimethylallylium-2-olate **373**.

Oxidation of thietan-3-one **375** with 3-chloroperbenzoic acid in dichloromethane gave the oxathiepinone-2-oxide **377** (Scheme 98).[229]

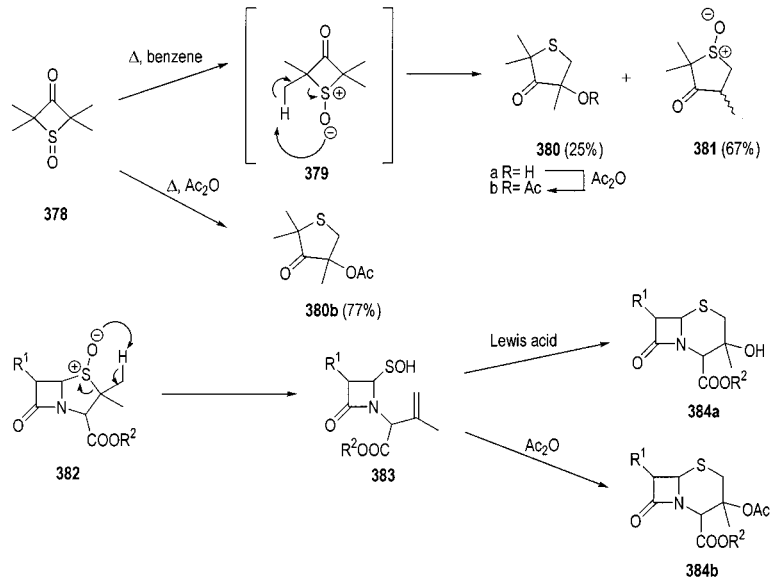
Probably, **377** arose from the intermediate thietan-3-one-1-oxide **376** that was further oxidized to the 1,1-dioxide and underwent a [2,3]-sigmatropic rearrangement.[229]

Finally, a thermal rearrangement of thietan-3-one-1-oxides has been described which showed some analogy to the ring expansion of penicillin *S*-oxides (Scheme 99).[254]

When heating thietan-3-one-1-oxide **378** in benzene, the products recovered from the reaction mixture were **380a** and **381**, in 25 and 67% yield, respectively.[254] In the penicillin series, it was shown that Lewis acids or acetic anhydride catalyzed the cleavage of the sulfur−oxygen bond in the transformation of **383** to **384a** or **384b**, respectively. Similarly, when the sulfoxide **378** was refluxed in acetic anhydride only the acetate **380b** was obtained in 77% yield.[254]

From the reactions and syntheses for thietan-3-ones, summarized in this chapter, it can be seen that its chemistry is in one way similar to the chemistry of azetidin-3-ones and oxetan-3-ones, but in another

Scheme 99



way also peculiar because of the nature of the sulfur atom. Moreover, the possibility to synthesize thietan-3-one-1-oxides and thietan-3-one-1,1-oxides from the corresponding thietan-3-ones broadens the scope of the reactivity of these compounds. It should be stressed that there are still possibilities in this area of research, since the chemistry of all these compounds overlap with each other.

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VI. References

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